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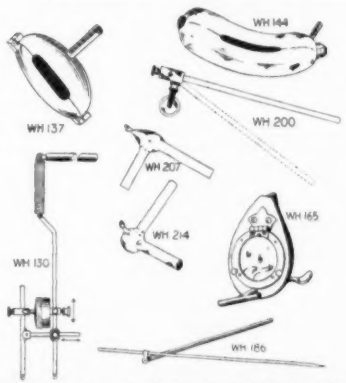

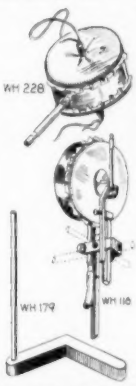

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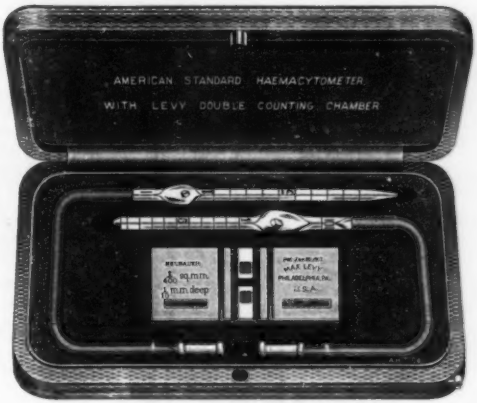

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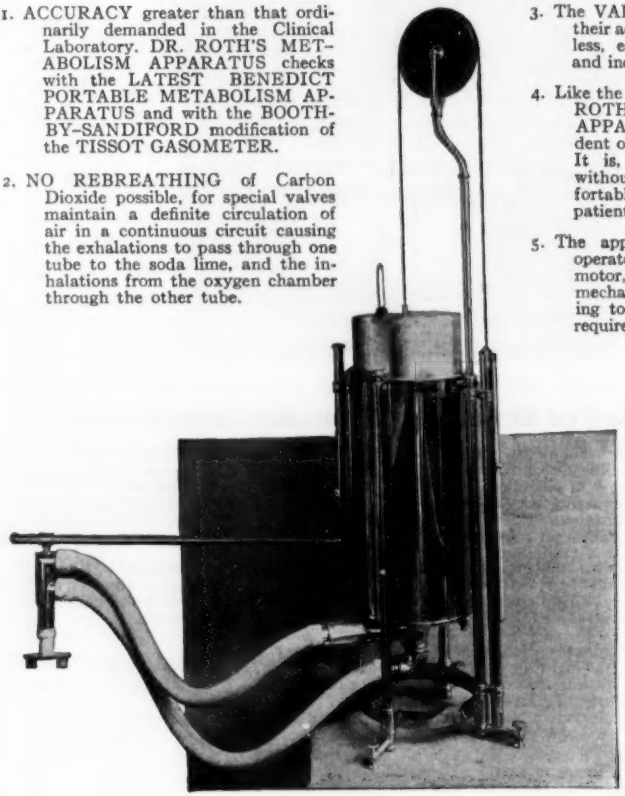

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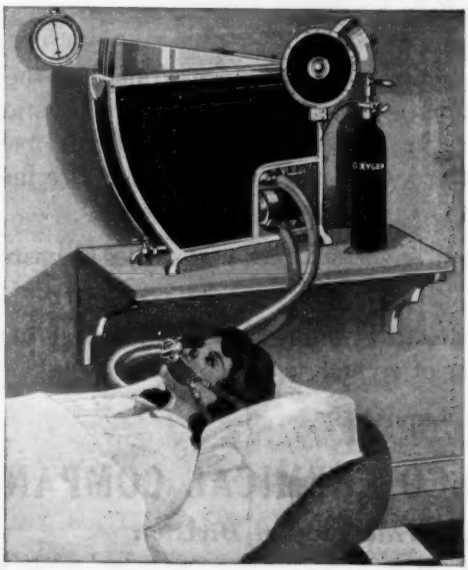

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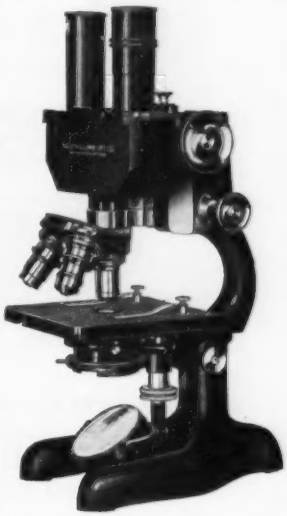

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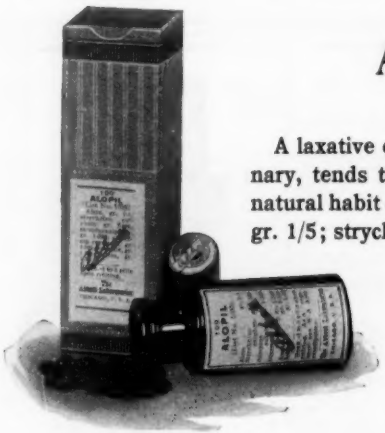

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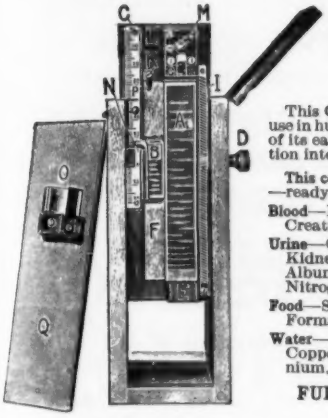

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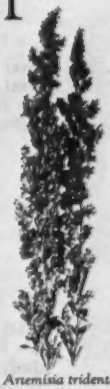

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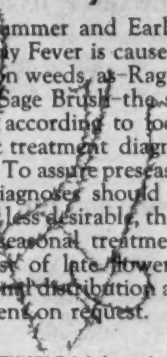

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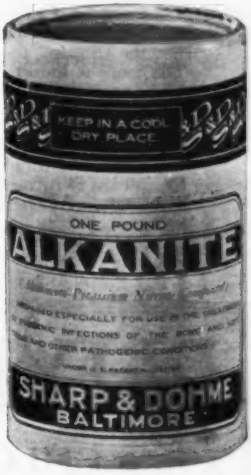

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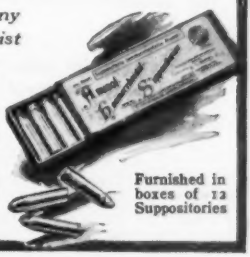

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OF THE MEDICAL SCIENCES

MAY, 1923

ORIGINAL ARTICLES.

TETANY IN THE ADULT, WITH SPECIAL REFERENCE TO ALKALOSIS AND CALCIUM METABOLISM.*

By Wilder Tileston, M.D.,

and

Frank P. Underhill, Ph.D.,

(From the Departments of Internal Medicine and of Pharmacology and Toxicology, Yale University, New Haven, Conn.)

Tetany in the adult occurs in two forms, one endemic in certain parts of Europe and apparently primary in character, the other secondary and occurring in the course of various morbid conditions, especially in connection with disease of the gastro-intestinal tract.

We have to report observations on 3 cases of tetany, all of the secondary form.

Case I.—*An Italian woman,† aged thirty-five years, suffering from Weil's disease with acute nephritis and acidosis, is given large amounts of sodium bicarbonate, with a diet poor in calcium. After nine days of alkali treatment, tetany develops, the CO_2 combining power of the blood having risen from 21 to 80 volumes per cent. Recovery.*

This patient, an Italian woman, aged thirty-five years entered the New Haven Hospital, December 17, 1916 (No. 60131), in the

* Presented at the Annual Meeting of the Association of American Physicians, May 2, 1922.

† Reported by one of us (Tileston) at the Annual Meeting of the Am. Soc. for Clinical Investigation, May 1, 1917, and cited by Palmer and Van Slyke, Jour. Biol. Chem., 1917, **32**, 499.

service of Dr. H. S. Arnold, to whom we are indebted for the privilege of reporting the case.

Past History. Was negative except for the occurrence of abortion in all of her four pregnancies (Wassermann negative).

Present Illness. The onset was sudden, with fever, ten days previous to admission. She was getting better when on the seventh day jaundice developed. There was diarrhea, with watery stools of a brownish color.

Physical Examination. At entrance showed a well developed and well nourished woman with fever (temperature 103.5°), marked jaundice, and enlargement of the spleen, which was palpable 3 cm. below the costal margin. The liver extended 3 cm. below the ribs.

The blood showed a leukocyte count of 17,200, of which 92 per cent were polymorphonuclears. There was a marked anemia of the secondary type, the red cell count being 2,800,000 and the hemoglobin 55 per cent (Talqvist). The stools were a bright yellowish-brown in color, and gave a very intense reaction for urobilin. The urine at entrance was clear and showed only the slightest possible trace of albumin, and no casts. Bile and urobilin were present in large amounts.

A few days after admission signs of acute nephritis developed, with albumin up to $\frac{1}{3}$ of 1 per cent, granular casts and red cells. The diagnosis of Weil's disease was made on the basis of the presence of the cardinal symptoms, viz.; febrile jaundice, enlargement of the spleen and albuminuria. No search was made for the spirochæta ictero-hemorrhagica.

The temperature fell by lysis, reaching normal on the thirteenth day of the disease, but it rose again two days later, owing to a colon bacillus pyelitis, the result of catheterization. Three days after admission, on December 20, there was nearly complete suppression of the urine, with air-hunger. The non-protein nitrogen of the blood on this day was 178 mg. per 100 cc and the phenolsulphonephthalein output (on the 25th) was only 10 per cent in two hours. The CO_2 combining power of the blood was 21 volumes per cent by the Van Slyke method, indicating a high degree of acidosis, the normal figures ranging from 50 to 60.

The next day the deep breathing continued, and an intravenous injection of 500 cc of a 5 per cent solution of sodium bicarbonate was made. The effect was striking, the dyspnea disappearing completely within twenty-four hours. The CO_2 combining power four hours later was 25.5, and on the 22nd, it had risen to 38. Sodium bicarbonate was given by the mouth, and on the 26th a second intravenous dose of 20 gm. was injected.

The non-protein nitrogen of the blood having risen to 212 mg., on the 26th, the patient was put on a diet poor in nitrogen, and incidentally, also very poor in calcium, with the intention of combating the azotemia. This diet consisted of 6 lemons, 200 gm.

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of sugar and 1000 cc of water per twenty-four hours. It caused vomiting, and on the 27th, nothing but water was given. On this day the CO_2 combining power was 80, indicating a considerable increase of the sodium bicarbonate. She had had in all 45 gm. of sodium bicarbonate intravenously and 83 gm. by mouth, in the course of nine days. The temperature was normal.

In the evening of the same day signs of tetany developed. Examination the following morning (the 28th) showed the elbows and wrists flexed and stiff, the fingers flexed at the metacarpophalangeal joints and extended at the others, the thumbs turned in and hyperextended; in short, the classical picture of tetany. The feet showed a similar condition. There was a marked Chvostek sign. Calcium lactate (gr. xx every four hours) and milk were prescribed. During the night of the 28th, two general convulsions occurred, accompanied by screaming. On the 29th, spontaneous spasm had disappeared, but Trousseau's and Chvostek's signs were easily elicited. By the first of January all signs of tetany were gone. The patient made a slow recovery, with gradual disappearance of the jaundice and of the splenic tumor, and was discharged convalescent February 11, 1917.

Discussion. An interesting feature was the remarkably high output of nitrogen in the urine, which began on December 25. During the six-day period from December 27 to January 2, no less than 318 gm. were excreted, or a daily average of 53 gm., on a diet of only moderate protein content. A high non-protein nitrogen of the blood, or "azotemia" has been noted of late in spirochetal jaundice by various French writers.

A somewhat similar instance of tetany occurring after the administration of soda was reported by Harrop[1] in 1919. His case, a colored woman, aged twenty-two years, was suffering from acute mercurial poisoning, with acidosis and suppression of urine. After two intravenous injections of sodium bicarbonate, totalling 60 gm., she developed tetany; the CO_2 combining power of the blood was 80 volumes per cent, and the calcium of the blood serum was "higher than 9 mg. per 100 cc, hence about normal."

Howland and Marriott[2] remark that it is not unusual for tetany to develop in children after the administration of soda for acidosis, and report 3 illustrative cases. In all of them, in contrast to Harrop's case in an adult, the calcium of the serum was much diminished.

Healy[3] saw a series of 6 cases of tetany, 4 of them fatal, developing after gynecological operations in women who had received enemata containing, by mistake, 80 gm. each of sodium bicarbonate. The patients received one enema immediately after operation, and a second four hours later. The 2 cases which recovered were treated with calcium.

Blum[4] recognized the danger of large intravenous injections of soda in diabetic coma, having observed 4 cases in which clonic and tonic spasms developed; though he did not mention tetany, it is probable that the condition was of that nature.

It is evident however that simply increasing the blood alkali is not sufficient to induce tetany; thus to a diabetic man under our observation, who had been operated upon for strangulated hernia, sodium bicarbonate was administered by rectum, to the amount of 49 gm. in two days, and the CO_2 combining power of the blood was raised to 86, yet tetany did not develop, nor could the signs of Trousseau and Chvostek be elicited. P. S. Henderson[5] was unable to produce tetany in children by giving large doses of soda, and the electrical reactions remained unaltered.

It is probable that a second important factor in the production of tetany in such cases is the presence of renal insufficiency, which has been noted in most instances.

CASE II.—*A woman, aged forty-six years, develops tetany following influenza. She is emaciated and suffers from intestinal indigestion with constipation. She has had two previous attacks of tetany. The CO_2 combining power of the blood is 77 volumes per cent, indicating a definite increase in the sodium bicarbonate. The serum calcium, estimated later during a period of latent tetany, is normal.*

Mrs. C., an American woman, aged forty-six years, was first seen by one of us, in the course of private practice, on March 30, 1919, at her home.

Family History. Unimportant.

Past History. She had had two previous attacks of tetany, both unrecognized. The first occurred five years ago while she was convalescing from grippe, the second one year ago after an enema, while suffering from intestinal indigestion. Twelve years ago she had valvular heart disease following acute articular rheumatism, and has been somewhat short of breath on exertion ever since. She has always been poorly nourished, and far from robust. Fifteen years ago she had nervous prostration, and four years ago mucous colitis.

Present Illness. Six weeks ago she had influenza, and has been in bed ever since. During this time she had been on an inadequate diet, very low in calcium, consisting of rice-gruel and Mellen's food, both made up without milk, and of broth. For eight days there was nausea, but no vomiting. The bowels were constipated, and had been moved by enemata. The last catamenia occurred in January (beginning menopause).

Twelve days ago she began to suffer from attacks of numbness and stiffness of the fingers, during which they became flexed. Four days ago, following an enema, she had an attack lasting two hours, in which the legs, arms and back got very rigid. Similar

seizures occurred after enemata, three days ago, and again this morning.

Physical Examination. Small, emaciated woman. The thyroid gland was normal. The heart was not enlarged; there was a loud, late systolic murmur at the apex, transmitted to the axilla and to the back. The lungs were negative except for an occasional sonorous rale. The abdomen was negative. The blood-pressure was 94 systolic, 70 diastolic. The superficial and deep reflexes were normal. Trousseau's sign was strongly positive; the Chvostek phenomenon was absent. The urine showed no albumin, sugar or indican; the stools were foul and constipated.

The CO_2 combining power of the blood on March 30, was 77 volumes per cent by the Van Slyke method (Dr. H. W. Haggard). This indicates a distinct increase of the sodium bicarbonate of the blood. The blood sugar was 0.1 per cent, by the Lewis-Benedict method.

The electrical reactions were taken later, and showed the following:

Date.	C. C. C.	A. C. C.	A. O. C.	CC tetanus.
May 16	0.8	1.8	1.2	3.5
May 25	1.0	1.9	2.1	4.0

The cathodal closing tetanus at less than 5 ma. may be taken as indicative of tetany, in the absence of organic disease of the central nervous system; the anodal reversal, while significant in young children, is not infrequently found in healthy adults. The patient was taking 40 grains of calcium chloride a day on the 16th, but the dose was probably too small to affect the reactions; on the 25th, no calcium had been taken for nine days.

The *serum calcium* on May 20, during a period of latent tetany, was 11.3 mg. per 100 cc by the Marriott-Howland method (Dr. L. J. Bogert). This is a normal figure. No calcium had been taken for four days.

The patient was put on a calcium-rich diet consisting of milk, cereals and spinach, and was given calcium chloride, 20 grains, four times a day. Under this regimen the major attacks ceased, but a condition of latent tetany remained, as shown by the occasional occurrence of slight spasms in the right hand, and by a slight Trousseau sign, when the dose of calcium was reduced.

The diet was gradually extended and the patient gained slowly in weight up to 105 pounds. A tendency to stiffness and numbness of the right hand persisted for several months. Up to the present time (1923) she has had no recurrence of tetany.

Comment. Points of interest are the moderate increase in the sodium bicarbonate and the normal figure for the serum calcium, the latter, to be sure, estimated at a time when the tetany was latent, not active.

It will be noted that two of the three attacks of tetany followed acute infections. The exciting cause of attacks was often the taking of enemata, possibly by reflex action from pressure on nerves while on the bedpan.

CASE III.—*An Italian woman, aged thirty-five years, has had for six months fatty diarrhea with marked loss of weight, following influenza. The cause of the diarrhea was not ascertained. Frequent attacks of tetany. Blood analysis shows a high sodium bicarbonate and very low calcium. Study of the calcium metabolism reveals distinct abnormalities. Large quantities of indican in the urine. Progressive emaciation and death four months after onset of tetany.*

A. B., an Italian woman, aged thirty-five years, was first admitted to the New Haven Hospital, April 25, 1919 (No. 71311), discharged May 18, readmitted June 3, (No. 71724) and discharged July 17, 1919. She was on the service of Prof. George Blumer, to whom we are indebted for the privilege of studying the case.

Present Illness. In October, 1918, she had influenza with pleuritic friction rub and persistent cough; she was in bed eight weeks and lost a great deal of weight. Previous to this time she had had diarrhea occasionally, but after the influenza, attacks of diarrhea became very frequent, accompanied by vague generalized abdominal pain, and alternating with short periods of constipation. About four weeks ago she began to have cramps in the feet, hands and neck, lasting for part of a day. Last menstruation four months ago.

Past History. Negative. There were six normal pregnancies.

Family History. Unimportant.

Physical Examination. On April 26 showed a small emaciated woman, weighing only 71 pounds (unimportant details are omitted). Temperature, pulse and respiration normal. The visceral examination was negative. The thyroid gland was small, the isthmus and left lobe were not palpable, the right lobe appeared smaller than usual. There was a constant fine tremor of the upper lip and of the left lower eyelid (later on both sides). Trousseau's sign positive on both sides. Chvostek's sign negative, but was obtained later. The knee jerks and Achilles reflexes absent with reinforcement, the plantar reflexes were also absent. (Later the knee-jerks were obtained, but much diminished.)

The electrical examinations are given below; they showed consistently cathodal closing tetanus with currents much under 5 ma.

Date.	C. C. C.	A. C. C.	A. O. C.	CC tetanus.
May 2	0.4	1.8	0.8	0.7
May 15	0.7	2.3	0.9	1.3
June 4	0.5	1.1	0.8	0.9
June 24	0.8	2.0	1.8	1.5
July 10	0.8	2.0	1.5	1.0

Laboratory Examinations. The blood Wassermann was negative. The urine was negative on routine examination.

Blood. The CO_2 combining power of the blood on April 30, was 90 volumes per cent by the Van Slyke method (Dr. H. W. Haggard), indicating a marked increase in the sodium bicarbonate. (The patient had been taking trifling amounts of soda, up to 2 gm. in twenty-four hours.) The serum calcium by the Marriott-Howland method was 6 mg. per 100 cc on May 10, and 5.4 mg. on May 14 (Dr. L. J. Bogert). Two normal controls showed 10 and 9.5 mg. respectively. The red count was 4,500,000 hemoglobin 68 per cent, leukocytes 10,200, differential count normal.

The stools were liquid throughout the patient's stay in the hospital, about three a day, with a strong rancid odor; they showed many globules of neutral fat and fatty acid crystals, many undigested muscle fibers but no starch. Pus and blood were absent. The trypsin content by the Gross method was 50 units and 250 units on two occasions.

Stomach contents one hour after an Ewald test breakfast: amount 40 cc, total acidity 22, free hydrochloric acid 7, lactic acid and blood absent.

The renal function was good, as indicated by a phthalein excretion of 70 per cent in two hours.

Roentgen-ray examinations of the gastro-intestinal tract and of the lungs were essentially negative.

A number of typical attacks of tetany were observed in the hospital, involving at first only the hands, which assumed the "accoucheur" position, later the feet also. The attacks were controlled at first by dilute HCl (f℥i, three times a day) which was not well tolerated, then by calcium chloride (30 grains, three times a day), for which calcium lactate (40 grains four times a day) was substituted later. A condition of latent tetany persisted, as indicated by the electrical reactions, and by the fact that the attacks recurred when calcium was omitted.

The tremor of the eyelids, so conspicuous a feature in the tetany following parathyroidectomy in dogs, was noted repeatedly, but disappeared under the administration of calcium.

Course of the Disease. The patient continued to lose weight regularly, and became extremely emaciated, the weight falling from 71 pounds on April 28, to 55 pounds on July 16. The diarrhea persisted, except for a period when she was at home for a fortnight between admissions. Large doses of pancreatin and calcium carbonate (45 grains of each three times a day) acted favorably, resulting in a formed stool, with disappearance of the rancid odor and of the acid reaction. But after a while the patient refused to take it, and it was omitted.

She left the hospital July 17, and died at home August 25, 1919. Permission to perform an autopsy was refused.

Diagnosis. The diagnosis of tetany is evident, and requires no discussion. The underlying cause was apparently an obscure disease of the gastro-intestinal tract associated with diarrhea. Disease of the pancreas seemed likely on account of the marked disturbance of fat absorption and the improvement with pancreatin. But the presence of trypsin in the stools in considerable amount is against complete absence of the pancreatic secretion, and in the absence of an autopsy the diagnosis must remain uncertain.

A study of the *calcium metabolism* was made, the details of which are published elsewhere.[6] Three five-day periods were employed, the first and last on a calcium-poor diet, the second on a diet rich in calcium by reason of the addition of milk. Two normal subjects under the same experimental conditions were available for comparison.

The *calcium balance* was slightly negative in the first period, but during the calcium-rich period there was a retention of nearly 3 gm. During the third (calcium-poor) period the stored calcium was partly eliminated, with a negative balance of 1.4 gm. The patient behaved with respect to the calcium balance like a normal person, except that there was a greater tendency to store calcium during the calcium-rich period, and to lose it during the succeeding calcium-poor period. This might indicate an instability in the regulation of calcium in tetany.

A comparison of the figures for the entire fifteen days showed a positive calcium balance of 1.3 gm. in the case of the subject with tetany, as opposed to negative balances of 2.9 gm. in each of the two normal controls.

These results might be taken to indicate a need for calcium on the part of this case of tetany.

The *absorption* of calcium was found to be normal.

The *elimination* of calcium, however, differed from the normal in that in all three periods there was a greatly diminished excretion by way of the kidneys. Thus in the controls 70 per cent of the intake was excreted in the urine during the calcium-poor periods, and 30 per cent during the calcium-rich period, while for the subject with tetany the figures were 10 per cent and 1 per cent respectively, the absolute amounts remaining practically constant at 22 mg. per day during all three periods.

A study of the fat absorption showed the utilization of fat to be very poor, being 78 per cent in the first period, 58 per cent in the second, and 59 per cent in the third. In other words, from 22 to 42 per cent of the fat intake was lost with the feces. These figures are comparable to those met with in total exclusion of the pancreatic secretion from the intestine.

Curiously enough, in spite of the diarrhea and emaciation, the nitrogen balance was positive throughout, and the absorption was unusually good, amounting to 98 per cent of the intake.

The urine analysis showed a high ammonia nitrogen, both relatively and absolutely, the average figures being 22 per cent and 1 gm. per day respectively. The high ammonia is difficult of explanation, for no other evidence of acidosis was to be found, either in the figures for p^H, or for total acidity and organic acids.

The large amounts of indican, indicating increased intestinal putrefaction, are also of interest. A detailed report is to be found in an article by Simpson.[7] It seemed as if the tetany were worse when meat was given and better when it was withheld, but owing to the coincident administration of calcium, these impressions are not conclusive. It has been noted that active tetany is more easily induced in dogs after parathyroidectomy if a meat diet is employed.

Stimulated by the reports of Paton and his coworkers,[8] search was made for guanidine in the urine, using Koch's method. None was found, but a beautifully crystalline salt was isolated in large quantities, which on analysis by P. A. Levene proved to be an ammonium gold salt.

General Discussion. In all of the 3 cases of tetany which we have studied, the sodium bicarbonate of the blood was abnormally high. This is easily explained in the first case by the administration of large amounts of soda. In the second and third cases it is not clear why the bicarbonate was increased. The work of MacCallum[9] is of interest in this connection. He showed that on ligating the pylorus, and removing the HCl by repeated gastric lavage, a condition similar to tetany developed, with marked increase in the blood bicarbonate and diminution of the chlorides; the tetany could be relieved by the administration of sodium chloride. Similar results were obtained by McCann[10] and by Hastings.[11] Loss of HCl by vomiting was not present in our last 2 cases; in the first it may have been a contributory factor.

It is important to note that an increased CO_2 combining power of the blood does not necessarily mean a change in the hydrogen-ion concentration toward the alkaline side, as the increase in bicarbonate can be, and in most cases probably is compensated, so that no change in the reaction of the blood takes place. The term "alkalosis" should be restricted to cases where the p^H of the blood is actually increased.

Interest in the possible relationship of alkalosis to tetany was started by the experimental work of Wilson, Stearns and Thurlow.[12] They found after parathyroidectomy in dogs that the onset of tetany was preceded by a decrease in the hydrogen-ion concentration of the blood, and followed by acidosis. The injection of acids or of calcium relieved the tetany. Their results have been criticized on account of the method employed (Barcroft's dissociation of hemoglobin method). Moreover, their results lack confirmation, for after parathyroidectomy Togawa[13] found acidosis in 10 of

11 dogs, as judged by the CO_2 combining power; Hastings and Murray[14] found a normal alkali reserve and normal p^H of the blood, and MacCallum in two dogs found no alkalosis.

Howland and Marriott[2] found in infantile tetany no increase in the CO_2 combining power of the blood and normal values for p^H.

With the exception of the cases of tetany following the administration of soda, already cited, we have found no published reports of increased CO_2 combining power of the blood in tetany. In future work on tetany of the adult it would seem desirable to determine both the p^H and the bicarbonate of the blood, as well as the calcium, and other elements (Mg, Na, K, P, S).

The relationship of decreased serum calcium to tetany, so well established by MacCallum[15] for tetania parathyreopriva, and by Howland and Marriott[2] for infantile tetany, remains obscure in the case of tetany of the adult, on account of the paucity of observations made by reliable methods. In our third case, and in that of Barach and Murray,[16] there was a notable decrease. In our second case (during a period of latent tetany) and in Harrop's case of tetany after soda, the serum calcium was normal. MacCallum[9] in experimental tetany following ligation of the pylorus found a normal concentration of calcium, and his results should be applicable to the gastric form of tetany in man. Also in the tetany resulting from hyperpnea a normal calcium has been found.

It appears, therefore, that some forms of tetany may occur without any change in the calcium concentration.

From the work of Loeb, Matthews and others* it appears that the excitability of the neuromuscular mechanism varies directly with the ratio $\frac{Na + K}{Ca + Mg}$, so that it is theoretically possible for increased irritability to result either from a decrease of the calcium, or an increase of the sodium. Kramer, Tisdall and Howland[17] have shown that in infantile tetany the increased irritability is due solely to the decrease of calcium, the concentration of magnesium, sodium and potassium in the serum being essentially normal. In the case of tetany following the administration of soda it is probable that the condition is due to the increase in sodium, the calcium remaining normal. Greenwald[18] believes that in these cases it is the increase in the Na ion and not that of the bicarbonate that is responsible.

Greenwald[19] in parathyroidectomized dogs found an increase of the phosphorus of the blood, and Binger[20] was able to produce tetany by the injection of neutral or alkaline phosphates in suitable amount. This was accompanied by a drop in the serum calcium to the extent found in infantile tetany. If, however, he injected *acid* phosphates, although the calcium figure fell to the same degree, tetany did not develop. Howland and Marriott[2] noted a marked

* For a discussion of the literature on this point consult the article by Kramer, Tisdall and Howland.[17]

decrease in the serum calcium, without tetany, in nephritis with acidosis. It is apparent therefore, that decrease of calcium is not enough of itself to cause tetany.

Kramer, Tisdall and Howland[17] found that in infantile tetany the phosphorus of the serum, though variable, was normal or only slightly increased in one-half of their cases. An increase in the phosphorus, therefore, cannot be an important factor in this form of tetany.

Recently Collip and Backus,[21] and Grant and Goldman[22] have noted the occurrence of tetany following overventilation of the lungs in healthy subjects. The urine showed a rapid fall in the titratable acidity, sometimes becoming alkaline, with increase of the basic phosphates and diminution of the ammonia. The blood revealed a decided decrease in the CO_2 combining power, and a definite increase in p^H (decrease in the hydrogen-ion concentration), while the calcium became somewhat increased. They explain the apparent anomaly of an "alkalosis" associated with diminished bicarbonate by the supposition that the CO_2 is washed out of the blood more rapidly than the alkali can be removed, which leads to a decrease of the ratio $\frac{H_2CO_3}{NaHCO_3}$.

Later Goldman,[23] and Barker and Sprunt[24] described tetany as a transitory condition in diseased persons as a result of attacks of hyperpnea. In our cases the tetany could not be attributed to this cause.

The attempts of Paton and his coworkers[8] to connect tetany following parathyroidectomy, and also as it occurs in man under natural conditions, with poisoning by guanidine has not met with confirmation, and owing to possible errors in the method employed, their results are open to question. It must be admitted however, that their production of tetany experimentally by injection of guanidine has been repeated by Watanabe[25] with positive results.

It is quite clear that there is still much to be learned as to the pathogenesis and the ultimate cause of this remarkable condition.

In conclusion it is interesting to note that some of the cases in the literature, and our third case, have been associated with a fatty diarrhea, usually of pancreatic origin; instances in point are the cases of Findlay and Sharpe[8] (almost the precise counterpart of our own), of Barach and Murray,[16] and of Bassett-Smith,[26] the last two occurring in sprue.

Summary. 1. An increase of the bicarbonate of the blood was demonstrated in 3 cases of tetany, 1 of which followed the administration of sodium bicarbonate.

2. A low serum calcium was found in 1 case, another showed a normal figure during a period of latent tetany, the case following soda was not examined as to calcium.

3. A study of the calcium metabolism in 1 case revealed definite abnormalities.

4. Large amounts of indican were found in the urine in 1 case.

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DIFFERENTIAL STUDY OF A CASE OF PULMONARY STENOSIS OF INFLAMMATORY ORIGIN (VENTRICULAR SEPTUM CLOSED) AND TWO CASES OF (a) PULMONARY STENOSIS AND (b) PULMONARY ATRESIA OF DEVELOPMENTAL ORIGIN WITH ASSOCIATED VENTRICULAR SEPTAL DEFECT AND DEATH FROM PARADOXICAL CEREBRAL EMBOLISM.* †

In Three Cases, Aged Respectively, Fourteen, Ten and Eleven Years.

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Pulmonary stenosis is one of the commonest of all findings in those forms of congenital cardiac disease characterized clinically

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by the symptom-complex of so-called congenital cyanosis. From the standpoint of etiology and anatomical structure, these cases may be divided into:

1. A small group in which the lesion is purely valvular and has resulted from an endocarditis of the pulmonary segments setting in during relatively late fetal life after the cardiac septa have closed. In these cases, which are considered here first as the less complex anomaly, there is a thickening and usually a fusion of the pulmonary cusps with the production of a small, often funnel-shaped, pulmonary orifice, which opens off the hypertrophied, but otherwise normal, conus of the right ventricle, and the pulmonary artery is usually of normal size, or may even be dilated; the interventricular septum is entire, but the foramen ovale is usually patent and is not infrequently fenestrated. These features prove the origin of the valvular lesion from the action of a fetal endocarditis setting in after the cardiac septa have closed.

2. In the other and much larger group of pulmonary stenoses the lesion is to be traced to an arrest of development in early embryonic life before the division of the heart into its four chambers is completed. In these cases, signs of fetal endocarditis as a complicating or even causative factor in early embryonic life may, or may not, be present but the main lesion is not inflammatory or valvular, but a true hypoplasia of the pulmonary tract, and the interventricular septum presents a defect at the base; while the aorta, which it will be remembered arises in early embryonic life from the *right* side of the common ventricle, usually appears displaced to the right arising from both ventricles above the septal defect, or entirely from the right ventricle; the pulmonary artery is usually small and thin-walled and the pulmonary valve bicuspid or rudimentary, and the conus of the right ventricle is narrowed, or it may (in cases where a septal defect communicates with the conus) be expanded below the cusps into a large chamber connected with the sinus of the ventricle by a constricted orifice (persistent lower bulbar orifice). These associated anomalies definitely prove that the pulmonary stenosis originated in early fetal life before the completion of the cardiac septa, from the operation of some cause which led to an early arrest or deviation of development, whereby an unduly small pulmonary artery has been cut off from a relatively large aorta, or the lumen of the conus of the right ventricle and the pulmonary orifice have become abnormally narrowed or otherwise deformed; and this combination, pulmonary hypoplasia, defect of the interventricular septum at the base, and *Rechtslage* of the aorta, is the commonest of all causes of congenital cyanosis in patients who reach the age of puberty.

The comparison of these two types of pulmonary stenoses and atresia with, and without, associated septal defect, yields considerable information of interest both from the clinical and pathological

standpoints. The following communication is based (1) upon the personal observation during life of a case of inflammatory pulmonary stenosis with closed septum (Case I cited below) and (2) the subsequent study of the heart of this patient after death and of the hearts of two other cases in the Pathological Museum of McGill University of (*a*) developmental pulmonary stenosis with associated septal defect and a superimposed inflammatory pulmonary valvular lesion (Case II), presented by Dr. P. P. Smyth of Big Valley, Alberta, and (*b*) developmental pulmonary atresia with associated septal defect and *Rechtslage* of the aorta (Case III) presented from the Pathological Service of the Montreal General Hospital.

The interpretation placed upon the findings in these 3 cases is amplified and corroborated by the results of a statistical study of 82 cases of pulmonary stenosis and 24 cases of pulmonary atresia made by one of us in another connection.[1]

In the 2 cases with associated ventricular septal defect a paradoxical cerebral embolism is suggested. In the light of the literature this surmise becomes a certainty. This interesting subject is discussed further below.

CASE I.—*Pulmonary Stenosis of Inflammatory Origin, Fusion of Cusps and Recent Verrucose Endocarditis. Pinhead Orifice. Ventricular Septum Closed. Patent Foramen Ovale. Death in Dyspneic Attacks.*

Clinical Data: D. S. L., female, aged fourteen years, admitted to hospital with severe dyspnea on exertion and marked cyanosis. Healthy and active until nine years old, when she began having repeated attacks of sore throat each winter. Cyanosis first became noticeable at this time; she became dyspneic on exertion and unable to play. After some three months in bed she improved, and for the next three years was able to attend school. In 1919 her cyanosis and dyspnea increased, and until her death the progress of the disease was steadily downward, and she was confined to bed much of the time. The cyanosis was noted especially about the nose, lips, fingers and toes; cough was troublesome but there was no orthopnea or dropsy. No history of chorea or acute rheumatic fever. Menstruation began at eleven years. Two sisters have dyspnea and palpitation but are of good color.

Physical examination showed a rather undersized girl with marked dyspnea and distinct cyanosis of the cheeks, nose, hands and feet. The mucous membrane of the mouth was a deep purple color. Marked clubbing of the fingers and toes. In the mouth there were many carious roots, and the tonsils showed much scarring and widely gaping crypts. The lungs were relatively normal. There was marked precordial bulging and pulsation; the maximum cardiac impulse being in the fourth left interspace 8.5 cm. from the midline. A rough systolic thrill was felt over the precordium with its maximum

intensity in the third left interspace, 5 cm. from the midsternal line. The relative cardiac dulness extended 4 cm. to the right and 10 cm. to the left of the midsternal line. The sounds were loud, regular and very rapid. At the apex, the first sound was very sharp but the second almost inaudible. The second sound was not accentuated at the pulmonic or aortic areas. A long, rough blowing systolic murmur was present at the apex, transmitted to the axilla and through to the angle of the scapula. It was also carried upward to the pulmonic area, its intensity diminishing as the clavicle was approached. The same murmur was audible at the aortic area and to a less degree in the vessels of the neck, and over the tricuspid area. At times there was a presystolic murmur inside the apex beat. Systolic blood-pressure 110, diastolic 60. The liver and spleen were not palpable. A trace of albumin was present in the urine. There was a moderate polycythemia; erythrocytes 7,600,000; leukocytes 22,000; hemoglobin 120 per cent (Sahli). The roentgenograph showed the heart slightly enlarged to right and left, with some fulness about the pulmonary artery. The electrocardiogram marked right-sided preponderance, with auricular hypertrophy.

Progress of Case During the six weeks preceding death the patient had two acute dyspneic attacks, attended with increased cyanosis, but was relatively comfortable during the intervals. She left the hospital and died August 30, 1921, during the third of these paroxysms. The autopsy was performed by Dr. C. T. Crowdy at the home of the patient. Only a small abdominal incision was allowed, through which the heart was removed without the larger vessels.

Description of Heart (W. W. B.) (Fig. 1). The heart of a young adult, greatly enlarged in its right chambers, the apex being formed entirely by the right ventricle. The right auricle is greatly dilated, and its wall is distinctly hypertrophied, and its columnæ carneæ are very prominent. There is a gaping foramen ovale admitting a lead pencil and three small fenestrations exist in the auricular septum along the posterosuperior border of the valvula foraminis ovalis where it joins the limbus Vieussenii. The tricuspid orifice measures 9 cm.; the cusps are slightly thickened and along their line of closure on their auricular aspect is a row of small irregular wart-like vegetations; the chordæ tendineæ are thickened and markedly shortened, the right papillary muscle being directly connected to the valve segment.

The right ventricle is greatly hypertrophied (wall 1.8 cm. thick), and its musculi pectinati and papillary muscles are enlarged and prominent. In its conus the musculature below the pulmonary valve presents a peculiar puckered condition appearing as if the chamber had been at one time of greater diameter, and its wall had been subsequently gathered in at the pulmonary orifice, forming

longitudinal pleats. There are six prominent crests and six clefts thus produced. The endocardium over these crests is greatly thickened, appearing as opaque white patches. Viewed from the ventricle, the rim of the pulmonary orifice at the base of the cusps measures 1.2 cm. in diameter.

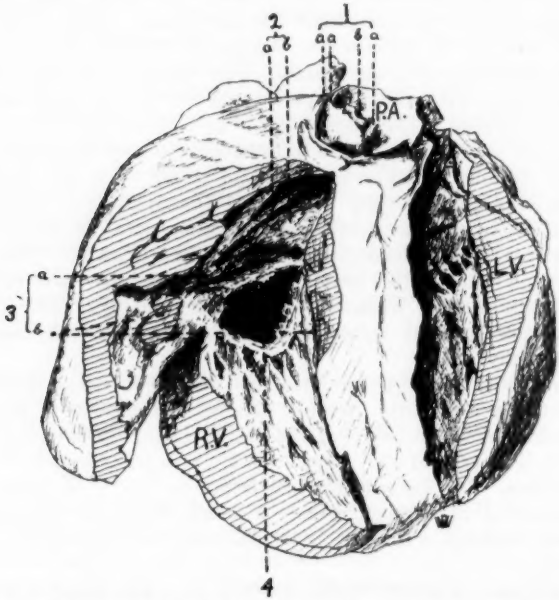

FIG. 1.—*Pulmonary stenosis of inflammatory origin, with fusion of cusps and pinhole orifice surmounted by a ring of warty vegetation.* (Case I). From a specimen in the Pathological Museum of McGill University presented by Drs. Lewis and Crowdy. (1) The fused cusps of the pulmonary valve with raphé *a*, *a*, *a*, showing the line of attachment to each other; *b*, central pinhole orifice with edges surmounted by a row of vegetations; (2) conus of right ventricle showing; *a*, puckering of musculature; and *b*, a white patch of thickened endocardium; (3) lower bulbar orifice formed by; *a*, crista supraventricularis; and *b*, trabecula septomarginalis (moderator band); (4) tricuspid orifice, edges of cusps thickened and surmounted by warty vegetations; *A*, aorta; *P.A.*, pulmonary artery; *R.V.*, right ventricle; *L.V.*, left ventricle.

The pulmonary artery is laid open above the valve; it is of about normal size (2 cm. in diameter), but is very thin-walled. The pulmonary cusps are symmetrically fused along their contiguous borders leaving a central circular orifice 2 mm. in diameter; this is surrounded by a firm brownish-pink colored rim, along the inner edge of which is a growth of small granular, grayish vegetations; the whole forms a structure resembling a partially expanded sea-anemone, the granulations appearing like the partly retracted tentacles. The "sea-anemone" is connected with the wall of the

pulmonary artery by three equidistantly placed firm fibrous ridges, 8 mm. in height. These are the remains of the attachments of semilunar cusps to the pulmonary artery. The left auricle is not altered in size or in thickness of wall. The left ventricle appears of normal size and thickness (walls average 1.3 cm.). The mitral orifice is 8.5 cm. in circumference. The aortic orifice measures 1.6 cm. in diameter. The aortic cusps are normal except for two small fenestrations. Both coronary arteries are double.

At the autopsy only a small abdominal incision was allowed. The great vessels, including the ductus arteriosus, were not removed from the body, but were cut away just above the heart, so that their condition cannot be discussed.

Museum Entry No. 7422. Presented by Drs. Lewis and Crowdy.

CASE II.—*Pulmonary Stenosis of Developmental Origin; Narrowing and Deformity of Conus, with Large Defect of Interventricular Septum. Aorta Displaced to the Right Arising from Both Ventricles above it. Fusion of Pulmonary Cusps and Stenosis of Orifice from Valvular Fetal Endocarditis. Patent Foramen Ovale; Phlegmon of Arm; Hemiplegia. Paradoxical Cerebral Embolism.*

Clinical Data (Dr. P. P. Smyth). Male, aged ten years, admitted to hospital with tender brawny swelling of left arm just above the elbow. Has had considerable cyanosis for some years, with dyspnea on exertion. His growth has been stunted and slight injuries have healed slowly. No history of any previous illness or of trauma to the arm.

Physical Examination. Temperature, 102° F. Pulse, 120. Poorly developed child, very marked cyanosis and clubbing of fingers and toes. Lungs and abdomen clear. Heart somewhat enlarged to right and left; sounds regular; soft presystolic murmur over the precordium. The left arm, just above elbow, showed a large fluctuating area, tender to the touch.

Progress of Case. The phlegmon on the arm was incised two days after admission and 100 cc of malodorous, blood-streaked pus was evacuated. Fever subsided under drainage, but the wound healed slowly. On the day of his discharge the boy became stuporous, and shortly afterward had a general convulsion followed by a left-sided hemiplegia. He was taken from hospital the next day but returned ten days later with a persistent left hemiplegia, stupor and incontinence of urine and feces. He passed into coma and died fifteen days after the first convulsion.

Description of Heart (W. W. B.) (Fig. 2). A child's heart of peculiar shape, being very broad transversely in comparison with its longitudinal measurements, and having a broad and flat apex, with a slight indentation (slightly bifid) formed chiefly by the right ventricle. Arising posteriorly at the middle of its base is a large thick-walled aorta, 2.5 cm. in diameter. The pulmonary artery, a

small inconspicuous vessel with very thin walls, about one-third the size of the aorta and measuring 1 cm. in diameter, arises in front of the aortic trunk, and curves across and around it upward and to the left.

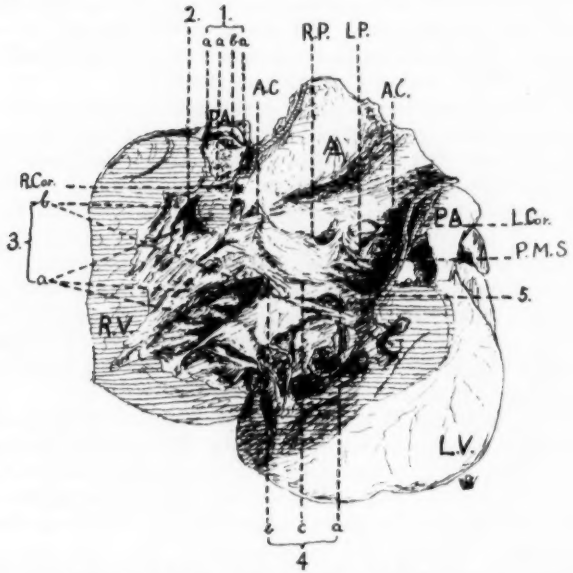

FIG. 2.—*Pulmonary hypoplasia of developmental origin, with inflammatory thickening and fusion of pulmonary cusps and stenosis of orifice. Large defect at base of interventricular septum. Rechtslage of aorta and displacement of pars membranacea septi to left of right posterior aortic cusp.* (Case II). From a specimen in the McGill Pathological Museum presented by Dr. W. P. Smyth, Big Valley, Alberta. (1) Fused cusps of pulmonary valve with raphé *a*, *a*, *a*, representing their attachments; *b*, central circular orifice; (2) hypoplastic and stenosed conus of right ventricle; (3) lower bulbar orifice formed by; *a*, crista supraventricularis here very thick; and *b*, trabecular septomarginalis here very short; (4) infundibular cusp of tricuspid valve with: *a*, chorda tendinea attached to posterior part of interventricular septum just below defect; *b*, chorda tendinea attached to rudimentary papillary muscle springing from crusta supraventricularis; and *c*, anomalous chorda running from right half of base of right posterior aortic cusp to free border of interventricular septum posteriorly; (5) free upper border of ventricular septum at defect. *P.A.*, pulmonary artery in two parts; *A.C.*, anterior aortic cusp, divided; *R.P.*, right posterior aortic cusp; *L.P.*, left posterior aortic cusp; *P.M.S.*, pars membranacea septi; *R.Cor.*, right coronary orifice; *L.Cor.*, left coronary orifice.

The left ventricle appears of about normal size. Near its apex is a peculiar branching aberrant chorda tendinea running from the interventricular septum to the base of the posterior papillary muscle. A second anomalous chorda arises from the apex of the same muscle and passes upward and forward toward the interventricular septum and is inserted posteriorly 1.5 cm. below the free border of a large defect in the base of the interventricular septum.

This defect measures 2 cm. in length; it begins posteriorly just in front of the pars membranacea and 2 mm. below the base of the right posterior (free) aortic cusp, opposite the junction of its middle and left thirds, and ends anteriorly 5 mm. behind the anterior (right coronary) aortic cusp opposite to the junction of its middle and left thirds. The defect is bounded below by the free superior border of the interventricular septum, which appears as a smooth rounded muscular crescentic ridge. The chordæ tendineæ of the aortic segment of the mitral valve do not connect with this border nor with the septum below it except for the single anomalous chorda mentioned above.

The wall of the right ventricle is greatly hypertrophied (2 cm. thick). There is a peculiar arrangement of the chordæ tendineæ of the infundibular cusp of the tricuspid valve, some of which gain an attachment to the posterior part of the interventricular septum just below the margin of the defect, others are attached to the anterior wall of the ventricle at the base of the right posterior aortic cusp opposite its right third, where they spring from a rudimentary papillary muscle, which had developed on the anterior surface of a large muscular column (crista supraventricularis) on the anterior wall of the ventricle, which passes downward toward the apex, and which apparently tended to conduct the blood passing from the right auricle through the right ventricle into the aorta by means of the septal defect. This muscular bundle serves to cut off the cavity in the right upper posterior angle of the right ventricle, which had developed into a large muscular shoulder. A few fibrous strands run from the right half of the base of the right posterior aortic cusp to the free border of the interventricular septum posteriorly.

The aorta arises about equally from both ventricles, riding over the septal defect; it is thick-walled and very large for the size of the heart, measuring 2.5 cm. in diameter.

The condition of *Rechtslage* or malposition to the right of the aorta is further made clear to the observer by noting the situation of the pars membranacea septi which usually lies at the base of the right posterior (free) aortic cusp and between it and the anterior (right coronary) cusp but in this case is seen to lie between the bases of the right posterior cusp and the left posterior (left coronary) cusp. The right posterior cusp is thus lying in front of, instead of behind, the pars membranacea septi, as in the normal heart.

The conus of the right ventricle leading to the pulmonary orifice is extremely small, appearing when viewed from below, as an elongated slit at the anterior upper angle of the right ventricle. It has thick muscular walls which form projecting pillars on the interior of the anterior ventricular wall, and a narrow, straight lumen which admits a probe 7 mm. in diameter, and it is lined with opaque thickened endocardium. Its opening into the ventricle is narrowed by the curving forward of the muscular bundles which form its

posterior wall. These represent the moderator band or trabecula septomarginalis medially and the crista supraventricular (Tandler[2]) laterally, the former of which is here much shorter than in the normal heart. The pulmonary orifice is guarded by a peculiar tubular sleeve-like structure which projects into the pulmonary artery for a distance of 1 cm. and which presents at its summit a circular orifice 4 mm. in diameter. This structure is attached to the walls of the pulmonary artery by three raphés, one on the right and the other two on the left side of the orifice; the first reaches the rim of the orifice and the latter two extend to within 4 mm. of this border and are separated at their attachment to the wall of the artery by an interval of 4 mm. This structure is formed of dense white tissue and represents the fused and thickened cusps of an irregularly divided three-cusped pulmonary valve (the left anterior cusp of which is abnormally small), which had evidently been the seat of a chronic fetal endocarditis. The pulmonary artery is very narrow and thin-walled.

The right auricle is dilated but not hypertrophied. The foramen ovale is patent by a valvular opening, admitting a lead pencil, and the posterosuperior border of the valvula foraminis ovalis, shows multiple small fenestrations. The Thebesian valve in the right auricle is represented by a thin thread-like strand which runs across the orifice of the coronary sinus.

Museum Entry No. 7431. Presented by Dr. P. P. Smyth, Alberta.

CASE III.—*Pulmonary Atresia with Associated Ventricular Septal Defect. Aorta from Conus of Right Ventricle. Patent Ductus Arteriosus. Hemiplegia. Appendicitis. Paradoxical Embolism. Cerebral Abscess.*

Clinical Data (Service of Dr. Hutchison, Montreal General Hospital). Male, aged eleven years, admitted to surgical service with severe abdominal pain, vomiting and fever. Had been a bluish color ever since birth; dyspneic on exertion, unable to run, but able to walk slowly. He was thought to have some form of congenital heart disease. Eight days before death the child began having convulsions with twitching of the hands and arms, the head being drawn to the left. Two days before admission he developed a severe pain in the right lower quadrant of the abdomen. Family history negative.

Physical Examination. There was marked cyanosis: definite clubbing of the fingers and toes. Pupils equal and active, tongue dry and coated. Lungs clear. Distinct precordial bulging, a diffuse apex beat and a definite thrill just inside apex beat. Heart extended from right border of sternum to 0.5 cm. beyond the left nipple. Sounds were regular, no accentuation of the first sound, but second was sharply cut and a little accentuated. Rough diastolic murmur at the apex, poorly transmitted toward the axilla. Pulse was full,

regular and well sustained. The abdomen showed some tenderness at McBurney's point, and rectal tenderness.

Progress of Case. The appendix was removed on the day of admission. Six days later patient complained of severe pain in head. Temperature 101° F. Pulse 96. Fever continued, but with slow pulse. The following evening he had a definite convulsion followed by a right sided hemiplegia; pupils equal, dilated, inactive double Kernig sign, Babinski on right. Smear of cerebrospinal fluid showed streptococci. Died at 10.30 P.M.

Autopsy (by Dr. Montgomery). This showed abscess of brain, left frontal lobe; acute purulent meningitis; congestion of the organs, recent appendectomy scar.

Description of Heart (W. W. B.) (Figs. 3 and 4). The heart of a child, rather broader than usual in proportion to its length. The apex is rounded and formed equally by both ventricles. There are a few petechial hemorrhages over the right ventricle. A large thick-walled vessel arises from the bulging conus of the right ventricle anteriorly in the position normally occupied by the pulmonary artery, and curves directly upward, giving off the vessels to the neck in their usual situation. This large vessel appears at first sight to be a common arterial trunk, but proves to be the aorta, for dissection in the tissues to its left reveals another very small trunk, the atresic pulmonary artery, arising blindly from the ventricular wall to the left and on a slightly posterior plane.

The aorta measures at its origin 5.5 cm. in circumference. Both coronary arteries are double and the innominate and left common carotid have a common origin. The ductus arteriosus is patent as a thin-walled vessel 1.5 mm. in diameter, arising from a funnel-shaped elliptical orifice 0.4 x 1 cm., guarded in the aorta on the right and left by two low, sharp-edged ridges. It opens into the right branch of the pulmonary artery, which is a vessel 5 mm. in diameter.

The pulmonary artery is a small thin-walled vessel measuring, just above the sinuses of Valsalva, 1 cm. in circumference and broadening out to 1.5 cm. above. Three rudimentary sinuses of Valsalva are recognizable but the cusps are represented only by thin, low, ridge-like folds. The musculature of the conus of the right ventricle is fused 5 mm. below the base of these rudimentary cusps and its lumen at this point is completely obliterated. From here for a distance of 7 mm. above the base of the cusps, the lumen of the pulmonary orifice and artery is occupied and occluded completely below, and partially above, by a cylindrical firm mass of pinkish-white tissue adherent to the posterior aspect of the wall (organized thrombus).

The aorta arises from both ventricles but chiefly from the conus of the right, riding over a defect in the base of the ventricular septum. This condition of "Rechtslage" of the aorta is further made clear by the abnormal relation between the aortic cusps and

the pars membranacea, which is the same as that noted and explained under Case II. (See page 643). The septal defect measures 2 cm. in length and is bounded below by the free crescentic upper border of the ventricular septum; this begins posteriorly 1 mm. in front of the pars membranacea septi, being separated from this by a band of musculature, and below the junction of the middle and left thirds of the right posterior aortic cusp, and extends anteriorly to

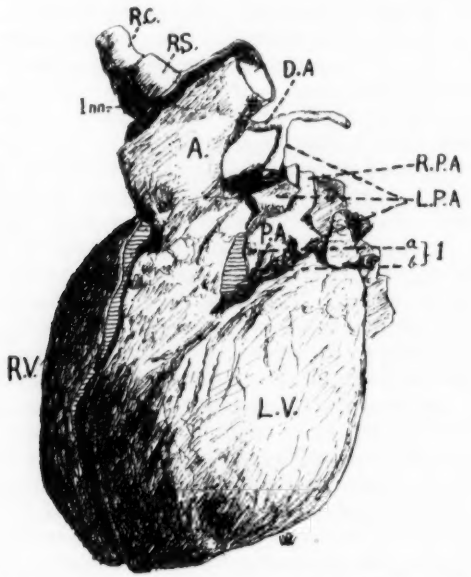

FIG. 3.—*Pulmonary atresia with hypoplasia of pulmonary artery and orifice, and closure of conus below cusps. Persistent lower bulbar orifice (conus a separate chamber). Patent ductus arteriosus; large defect of interventricular septum at base and Rechtslage of dilated aorta.* (Case III). Left anterior surface; heart enclosed: to show relative sizes and position of dilated aorta, atresic pulmonary artery and patent ductus. From a specimen presented to the McGill Museum by Rhea and Montgomery, Montreal General Hospital; (1) Pulmonary orifice obliterated below; *a*, rudimentary sinuses of Valsalva and *b*, partly filled by an organized thrombus; *L.P.A.*, left pulmonary artery divided; *R.P.A.*, right pulmonary artery; *D.A.*, ductus arteriosus patent; *R.S.*, right subclavian artery; *Inn.*, innominate artery; *R.C.*, right common carotid artery.

the cleft between the left posterior and anterior cusps. The left ventricle is dilated and its wall is 8 mm. thick.

The right ventricle is elongated and narrow and greatly hypertrophied. The conus is demarcated from the rest of the cavity by a thick muscular cushion running from the anterior part of the interventricular septum at a point midway between base and apex of the heart, backward and to the right to the middle of the insertion of the right posterior aortic cusp whence it curves forward and down-

ward to the right to the anterior wall producing a semilunar orifice (lower bulbar orifice) 2.2 cm. long leading from the cavity of the right ventricle into the conus. This cushion represents the much accentuated moderator band of the trabecula septomarginalis below, and the crista supraventricularis (Tandler[2]) above, which are present in the normal heart but are less prominently developed. The conus thus forms a separate chamber above the orifice with a

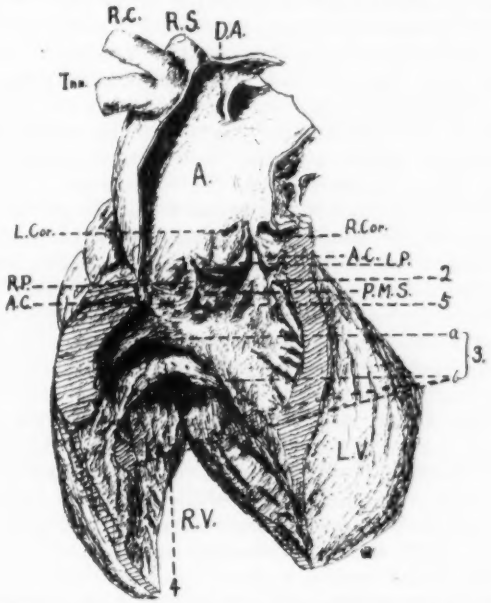

FIG. 4.—*Pulmonary atresia with large defect of interventricular septum at base and Rechtslage.* Right posterior view of the same specimen (Case III) shown in Fig. 3, right ventricle and aorta laid open to expose the interior. (1) (See Fig. 3); (2) obliterated upper part of conus of right ventricle; (3) lower bulbar orifice formed by; *a*, crista supraventricularis; and *b*, trabecular septomarginalis, which form a prominent muscular ridge; (4) infundibular cusp of tricuspid valve; (5) free upper border of ventricular septum at defect; *D.A.*, aortic orifice of patent ductus; *R.C.*, right common carotid, and *Inn.*, innominate artery arising by common trunk; *L.Cor.*, double left coronary; *A.C.*, anterior aortic cusp divided; *R.P.*, right posterior aortic cusp; *L.P.*, left posterior aortic cusp; *P.M.S.*, pars membranacea septi.

thick anterior muscular wall 8 mm. thick. On its superoposterior wall it opens into the aorta by an elliptical orifice 2.2 x 1.5 cm. in diameter.

The conus of the right ventricle ends superiorly and to the right as a blind funnel-shaped cleft in the musculature which represents the obliterated communication with the pulmonary orifice. This cleft is 8 mm. below the anterior aortic cusp and 6 mm. below the anterior limb of the crescentic border of the ventricular septum.

Presented by Dr. Rhea, Museum Entry No. 7286.

Discussion. A. Pathological Anatomy. Three interesting anatomical points must be emphasized in connection with Cases II and III. (*a*) *The deviation of the aorta to the right, "Rechtslage,"* whereby this vessel rides above the defect rising from the right as well as from the left ventricle, and which is shown in both specimens by the relation of the aortic cusps to the pars membranacea septi. That this is not a deviation of the position of the pars membranacea instead of the aorta as might be thought, is plainly seen in both cases from the fact that on viewing the pars membranacea from the right auricle it is seen to be in its normal situation, *i. e.*, at the base of the medial cusp of the tricuspid valve just posterior to the angle between it and the infundibular cusp, half in the auricle and half in the ventricle. (*b*) The defect in the interventricular septum is not in exactly the same situation in the two hearts, being placed more posteriorly in Case II, than in Case III. This is shown by the fact that in Case II, the defect in the septum leads into the main cavity of the right ventricle being almost entirely behind the crista supraventricularis and only slightly involving this band of muscle. This position of the defect posteriorly is evidenced also by the fact that several of the chordæ tendineæ of the tricuspid valve take their origin from the septum near the edge of the defect. Viewed from the left ventricle the defect impinges directly on the anterior border of the pars membranacea septi. In Case III on the other hand, the defect in the septum leads into the conus of the right ventricle being wholly in front of the crista supraventricularis and, therefore, having no relation to the insertions of the chordæ tendineæ of the tricuspid valve. Viewed from the left ventricle, the defect in the septum is seen to be separated from the anterior edge of the pars membranacea septi by a band of septal musculature about 2 mm. in width and is thus proved to be more anterior than in Case II. (*c*) In Case II, the whole conus is hypoplastic, being much smaller than normal, while in Case III, the conus is as large as, or larger than normal, but is completely aplastic above and is demarcated below from the sinus of the right ventricle by the hypertrophied muscle bands (crista supraventricularis and trabecula septum marginalis) which mark the site of the lower bulbar orifice of the embryonic heart; thus presenting the condition described by Keith[3] as "conus a separate chamber."

The difference in the development of the conus in these 2 cases may be explained by comparing the work that each evidently was called upon to perform. In Case II, the pulmonary orifice was very small and as the defect in the septum did not open into the conus, it is evident that the amount of blood which the conus was called upon to look after was relatively small. Therefore, it did not increase in size and eventually became an unimportant structure as the rest of the heart developed. In Case III, on the other hand, although the pulmonary orifice was not patent, still the defect in

the septum opened into the conus and all the blood from the right side of the heart had to traverse the conus before it could enter the aorta. The conus thus was called upon to perform considerable work, and this is reflected in its spacious lumen and thick muscular walls.

B. Pathological Physiology and Clinical Aspects of the Cardiac Lesions. 1. *Cyanosis and Dyspneic Attacks.* As was stated above the clinical picture of pulmonary stenosis or atresia is that of a true *morbus ceruleus*, the patients presenting, in varying degree, but in classic pronouncement, the cyanosis, clubbing, dyspnea and polycythemia that are the expression of deficient aëration of the blood. The prominence and constancy of these manifestations in all cases is explained by the fact that interference with the pulmonary circulation, which is here the pathological condition *per se*, is by far the most serious cause of insufficient oxygenation; a direct admixture of the venous with the arterial stream, such as occurs in a septal defect with raised pressure in the right ventricle, being of quite secondary importance, although of course this is, when present to a sufficient extent, also a factor.

The cyanosis varies in intensity and the date of its appearance, not only with the degree of narrowing of the pulmonary tract, but also with the presence or absence of a defect of the interventricular septum, which introduces a factor of very different clinical significance in the two conditions of (*a*) stenosis and (*b*) atresia of the pulmonary tract.

In *pulmonary stenosis*, where a less acute grade of obstruction exists than in the atresias, cyanosis naturally tends to be less severe and is usually absent at birth, appearing only after the first weeks or months, or in some cases (usually those with closed septum), years of life. Here we find, however, that *an associated defect of the interventricular septum* introduces a mechanical complication that increases the difficulties of the pulmonary circulation and so *intensifies the seriousness of the lesion.* For such a defect in the first place permits the escape of a certain amount of blood from the right to the left ventricle during the heart's systole, and thus reduces the volume of the blood to be transmitted from the right chamber to the lungs through the stenosed pulmonary orifice; and, secondly the venous blood so transmitted enters the arterial stream, thus bringing in another factor to further diminish the lowered oxygenation under which the patient is suffering. In the more favorable condition of pulmonary stenosis with *closed* ventricular septum, the entire force of the right ventricle is expended on pushing the venous blood through the narrowed pulmonary tract; the foramen ovale which is usually patent in these cases appearing to offer less mechanical interference with the development of pressure in the conus of the right ventricle.

A statistical analysis of 83 cases of pulmonary stenosis with

autopsy findings in the literature gives the following corroboration of the above statements. Among 19 cases of *pulmonary stenosis with closed septum*, cyanosis was entirely absent in 5; was "slight" or "transient" in 5 others; "moderate" in 3, and in only 2 cases was it "marked." The average duration of life in these 18 cases was *twenty-one and three-tenths years*, the youngest age at death *four*, and the oldest *fifty-seven years*. Case I of this communication is an example of this combination; here cyanosis did not appear until the ninth year, and only became marked with the progress of the inflammatory process, which finally reduced the pulmonary orifice to pinhead size. On the other hand, among 64 cases analyzed of pulmonary stenosis with associated septal defect, the aorta in most cases displaced to the right and, arising from both ventricles above the defect, cyanosis was remarked upon as being "slight" or "absent" in only 4 cases, and was "marked" in 37. The average duration of life in these 64 cases *was eight and seven-tenths years*, the youngest patient dying in infancy at eleven days and the oldest at twenty-eight years. *These figures are conclusive.* Case II of this communication is an example of this more serious and much more frequent type of pulmonary stenosis.

In the group of *pulmonary atresias* an interesting variation from that in pulmonary stenosis is to be observed in that an *associated septal defect* alleviates instead of aggravating the condition, by providing another channel to the lungs for the aërated blood which is here unable to pass through the completely obliterated pulmonary lumen. Especially where the aorta rides over the defect or arises entirely from the right ventricle, we have the greatest amelioration possible, for the current from the right ventricle passes directly into the aorta and thence through a patent ductus to the lungs. Such cases may live to puberty and may be indistinguishable clinically from the graver forms of pulmonary stenosis. A closed or merely slit-like foramen ovale appears further to mitigate the situation, possibly by leaving a greater volume of blood in the right chambers to be transmitted directly into the aorta through the defect. Case III of this communication is an excellent illustration of this relatively most favorable combination in pulmonary atresia, for the aorta arose from the conus of the right ventricle above a large defect in the septum, and the foramen ovale, though patent, was very small. The patient, a well-developed boy, aged eleven years, died of an intercurrent complication (cerebral abscess). Among 18 cases of *pulmonary atresia with defective ventricular septum* analyzed, the average duration of life was three and seven-tenths years, the maximum age at death in the recorded cases analyzed being thirteen years.

On the other hand, *pulmonary atresia* with *closed interventricular septum* is incompatible with life beyond the first weeks or months. The patients are a deep mulberry hue at birth and die in infancy.

Of 6 such cases all died with this intense grade of cyanosis at ages varying from *six days* to *six months*, the average age at death being sixteen weeks. These figures are conclusive.

The following table summarizes the foregoing statements:

Nature of lesions.	Number of cases.	Marked cyanosis.	Maximum age.	Average duration.	Precordial thrill.*
Pulmonary stenosis:	83				
(*a*) With closed septum	19	In 2	57 yrs.	21.3 yrs.	In 7
(*b*) With ventricular septal defect	64	In 37 (57.8%)	28 yrs.	8.7 yrs.	In 10
Pulmonary atresia:	24				
(*a*) With closed septum	6	Extreme in all	6 mos.	16 wks.	1
(*b*) With ventricular septal defect	18	In 11	13 yrs.	3.7 yrs.	1

Dyspneic Attacks. Many of these patients, the subjects of congenital cyanosis, have alarming attacks of dyspnea usually accompanied with temporary increase of the cyanosis, which is often intense. During these attacks there may be loss of consciousness and our first case (pulmonary stenosis with closed septum, the pulmonary orifice of pinhead size) died during one of these paroxysms. There seems to be a curious relationship between the severity of these attacks and the extent of the ischemia in the pulmonary circulation. In another case very similar to our Case I of a pulmonary stenosis with minute orifice (2 mm. wide) and closed ventricular septum reported by Cassel,[4] the patient also presented typical dyspneic attacks of great severity, the cyanosis being absent between the paroxysms during the early part of the illness. Dyspneic attacks with a transient cyanosis are a characteristic symptom also of patent ductus arteriosus, and are probably synchronous here with a temporary reversal of flow, during excitement or exertion from the pulmonary artery to the aorta, through the lumen of the patent vessel. In view of this fact, the special prominence of such attacks in these 2 cases of pulmonary stenosis with pinhead orifice and closed septum appears significant of their explanation as the expression of a temporary acute pulmonary ischemia.

Polycythemia of a moderate grade was present in our Case I, the only one of the three in which a blood count was made. *Hippocratic fingers*, or *clubbing both of fingers and toes*, was present in all three. In Case I the nose was slightly clubbed also.

2. *Atypical Physical Signs.* A *precordial thrill* is of frequent occurrence in pulmonary stenosis and appears to be more frequent in the cases without a defect of the interventricular septum. In a series of 83 cases (M. E. A.) of pulmonary stenosis, a thrill was noted

* This column is from an analysis published elsewhere, and the figures are referred to below.

in 8 out of 19 patients showing an intact septum at necropsy, while a thrill was absent in all but 10 of the 64 patients in whom there was an associated septal defect. (See fifth column in Table above). In our first case as also in that by Lallemand (see below), in both of which the ventricular septum was intact, a marked precordial thrill existed, while in Case II with patent interventricular septum, no thrill was noted. In our third case (pulmonary atresia) the marked thrill that was present was localized near the apex and was undoubtedly produced by the large septal defect and not at the pulmonary orifice.

Murmurs and Accentuations. In this connection the following generalization may be made. In pulmonary stenosis the pulmonary second sound is usually not accentuated and it may be almost inaudible; a rough systolic murmur is practically always present and is usually of maximum intensity over the pulmonary area and transmitted upward along the course of the pulmonary artery; this murmur may be heard loudly over the entire precordium but is usually fainter below, and may be inaudible at the apex and to the right of the sternum; with a patent foramen ovale it may take on a diastolic-systolic phase, or a second murmur, often presystolic in rhythm and variable in its occurrence, may be introduced, with maximum intensity at the third and fourth left interspaces. In an associated septal defect this second murmur has a similar localization, but is more definitely systolic in rhythm, is usually heard also in the left interscapular region and may be propagated, when combined with a pulmonary stenosis, along the aorta into the carotid arteries in the neck (Eisenmenger[5]).

In Case I of this communication (pulmonary stenosis with closed ventricular sepum and patent foramen ovale), the little patient was under the personal observation of one of us (D. S. L.) both in hospital and in private for the last eight months of life and the findings were confirmed by repeated examination. The physical signs are of much interest, not only as illustrating certain characteristic features, namely, the absence of pulmonary accentuation, the presence of a coarse systolic thrill and murmur diffused over the precordium (originating at the pulmonary orifice), and a fugitive presystolic murmur (generated at the patent foramen ovale); but also as emphasizing the fact that it is difficult and frequently impossible to diagnose during life between the various forms of cardiac defects, and especially between these two types of pulmonary stenosis. For here the point of maximum intensity of the thrill (third and fourth left interspace) and the localization and direction of transmission of the murmur (at apex and into the back and vessels of the neck) pointed to an associated ventricular defect, although none was present.

C. Paradoxical Cerebral Embolism. Two of the cases whose histories form the subject of this communication (Cases II and III),

both deeply cyanosed subjects, died with unexpected manifestations of a cerebral complication of apparently identical nature, a hemiplegia ushered in by pain in the head, convulsions, stupor and elevation of temperature, death following on the fifteenth and eighth days respectively after the onset of symptoms. In both cases operation upon an inflammatory focus in another part of the body (evacuation of a phlegmon of the arm in Case II and appendectomy in Case III) had taken place shortly before the development of cerebral symptoms. The autopsy in Case III revealed a large abscess of the left frontal lobe and purulent meningitis; in Case II the brain was not examined but a similar condition may fairly be concluded. In both patients the hearts showed a defect of the interventricular septum and a deviation to the right of the aorta, which arose from the right ventricle, thus presenting an easy route for a septic embolus from the thrombosed venules of the periphery to the terminal arteries of the cerebral circulation (paradoxical or crossed embolism).

This combination of events in these two cases, is of interest from several aspects. In the termination by *cerebral abscess* it illustrates in the first place an outcome of congenital cardiac lesions that is far from infrequent, and that was recognized by the older English students of the disease as a part of its classic picture; and they present, in the occurrence of a *paradoxical embolism*, one of the best examples we have of the manner in which the apparently bizarre symptomatology of cardiac defects is reduced, in the light of a complete knowledge of all the facts, to conditions of perfect simplicity. Moreover, the apparent contradiction of an established physiological law by the earliest observations upon the phenomenon of paradoxical embolism, and the subsequent explanation of these by the demonstration of a communication between the two circulations through a defect in the cardiac septum, is a dramatic episode in the history of pathological anatomy in the nineteenth century which claims our instant attention.

Historical. One of the most important of Virchow's early contributions to medical science (1845) was his elucidation of the nature of embolism, as the carrying in the blood stream of fragments broken off from the parent thrombus to the infarction of distant tissues. In a subsequent research, Rindfleisch (1873) pushed these investigations further to the conclusion that an embolus must always go forward in the path of the circulation and that emboli in the right heart or in the lung must, therefore, be derived from the venæ cavæ or their tributaries, and those in the end arteries of the systemic circulation from the radicals of the pumonary veins or the left heart. He explained certain apparent contradictions by supposing that occasionally small emboli could traverse the capillaries of the lung and be stopped in the narrow end arteries of the kidney and other organs. Trousseau (1880) in speaking of ulcerative

endocarditis as a cause of cerebral embolism, related a case in which the valves of the right heart only were affected, and suggested that the vegetations had traversed the capillary vessels of the lung by means of ulcerating through the wall of the pulmonary arterioles. The observation made by Hirschberg[6] that cerebral abscess is especially common in gangrenous inflammatory processes in the lungs where there is extensive destruction of tissue may indeed have some such explanation.

The first to trace definitely the path of the embolus through an opening in the cardiac septum was Cohnheim (1877), who demonstrated a recent embolism of the right Sylvian (middle cerebral) artery in a case of widely patent foramen ovale with thrombosis of the veins of the lower extremities, but the valves of the left heart, aortic arch and arterial system proved absolutely free from any thrombus. Litten next, in 1880, autopsied a case of gangrene of the right leg from a large embolus blocking the femoral artery, but was puzzled to account for this and for numerous small infarcts in spleen and kidney, in the absence of any source in the arterial circulation, and finally submitted the organs to Virchow, who demonstrated a patent foramen ovale and thrombi in the right auricle. The conclusions enunciated by Cohnheim and Virchow on the basis of these two cases were substantiated and verified by Zahn[7] (1881), who discovered, in a case of extensive thrombosis of the iliac veins of puerperal origin, a long embolus of pen-handle size sticking through a patent foramen ovale into the left auricle. A similar observation was made by Hauser.[8] In a full analysis of 711 subsequent autopsies in Zahn's service made by his assistant Rostan,[9] the foramen was patent 139 times; in 3 of these cases its orifice was occluded by a thrombus, and in 7 a so-called paradoxical embolism had taken place through it. Of these 7 cases, in 3 the embolism was cerebral. Metastases of tumor masses through a patent foramen were later demonstrated by Zahn;[10] particles from ruptured liver by Schmorl, and the vegetations of malignant endocarditis by Jaeniche, Sänger and others. The above details are cited in a full review of the literature to 1907 as given by Ohm,[11] with the report of a case of his own of patent foramen ovale, thrombosis in the hemorrhoidal veins and two successive attacks of cerebral embolism, the first three weeks before death followed by a left hemiplegia and softening in the left lenticular nucleus and the second a blockage of the right middle cerebral artery, followed by immediate exitus.

Cerebral Abscess. The most interesting publication in connection with the present communication is that by Ballet[12] entitled, "*Des abscès du cerveau consecutifs à certaines malformations cardiaques.*" He collected from the literature 4 cases and published 1 of his own, of cerebral abscess in patients whose hearts showed a communication between the right and left chambers; in 1 (Lallemand) there was a widely patent foramen ovale and pulmonary stenosis of the

inflammatory type; in 2 (Ballet, Louis) a ventricular septal defect without other cardiac anomaly; and in 2, those by Farre[13] and Berthody, a condition similar to the authors' Case II of defect at the base of interventricular septum aorta displaced to the right and arising from both ventricles above this and pulmonary hypoplasia. The autopsies in these 5 cases were not detailed and the state of the peripheral veins is not mentioned nor was the possibility of a crossed embolism apparently considered by Ballet, but a causal connection between the cerebral and cardiac lesions was definitely assumed. Stone[14] and Peacock[15] report similar cases. The latter remarked that a cerebral complication is the commonest cause of death in congenital cyanosis, but he also did not try to establish the nature of the etiological sequence which he believed existed.

Several cases of sudden onset of cerebral symptoms followed by death in congenital heart lesions are reported from the clinical standpoint in which a paradoxical embolism may fairly be assumed. Thus Palmer[16] relates the onset of a hemiplegia in a woman, aged twenty-two years, with cyanosis, clubbing, polycythemia and dyspnea in whom physical examination showed a congenital heart lesion. When it is realized how frequent is the occurrence of thrombosis of the right heart and peripheral veins, how direct is the path to the systemic circulation that is presented by a defective septum, especially when associated with deviation to right of aorta, and the fact that small emboli, which would end in the production of relatively harmless infarcts elsewhere in the body, will inevitably lead, on their arrival in the end arteries of the brain, to serious symptoms indicating the disintegration and frequently the septic infection of the delicate nerve tissue, we understand the grave significance of septal defects in this connection.

In further illustration of this interesting subject the 14 cases of cerebral abscess in cardiac septal defect enumerated above, are here summarized:

A. *In defect of interventricular septum.*

(*a*) *Without other anomaly.*

1. *Louis. Arch. gen. de med.* (*quoted by Ballet*), male, aged twenty-five years. Defect V. S. at base, smooth margins. No other anomaly. *Two areas of cerebral softening.* (*a*) In anterior part of corpus striatum, and (*b*) in optic tract behind this.
2. *Ballet. Arch. de med.* (1880, **5**, 659), own case, male, aged fifteen years. Defect V. S. at base, malposed septum, aplastic right ventricle, and tricuspid orifice. *Abscess in frontal lobe of brain and purulent infiltration.* Nasal fossæ, bones of cranium and meninges elsewhere free from inflammation. Left hemiplegia twelve days before death.

(*b*) *With deviation to right of aorta and pulmonary stenosis.*

3. *J. R. Farre. Obs.* 3 *in "Malformations of Human Heart," London,* 1814, male, aged nine and a half years. Aorta from both ventricles, pulmonary orifice small. Open between ventricles below aortic cusps. *Abscess in right hemisphere of brain containing ½ ounce of thick pus.* Cyanosis from two and a half years. Left hemiplegia eight days before death.
4. *Berthody. Medical Examiner, May,* 1845, female, aged twenty-one years. V. S. interrupted just below aortic cusps. Pulmonary artery hypoplastic. *Abscess in left posterior lobe of brain* size of pigeon's egg, left lateral ventricle filled also with pus. Slight cyanosis and dyspnea throughout life. Delirium and coma before death.
5. *Stone. St. Thomas' Hosp. Reports,* 1881, **11**, 57. Female, aged nineteen years. Conus stenosis of right ventricle. Acute endocarditis of lower conus orifice. Large defect V. S. at base. Purulent meningitis. *Old cerebral abscess in right occipital lobe containing fetid pus;* burst into horn of right lateral ventricle. Cyanosis and dyspnea from birth. Sudden onset of severe headache. Death.
6. *Peacock. Trans. Path. Soc., London,* 1881, **32**, 65. Male, aged six years and nine months. Aorta to right from both ventricles. Defect V. S. at base. Pulmonary hypoplasia. F. O. closed. Brain not examined. Cyanosis, clubbing from birth. Left hemiplegia with convulsions setting in with pain in head and stupor sixteen days before death. Temperature 101° F.
7. *Authors' Case II* (*this article*). Male, aged ten years. Pulmonary stenosis, defect V. S. at base deviation to right of aorta. Brain not examined. Cyanosis and dyspnea, clubbing, phlegmon of arm evacuated, left hemiplegia followed and death fifteen days later.
8. *Authors' Case III* (*this article*). Male, aged eleven years. Pulmonary atresia. Defect V. S. at base. Aorta from conus of right ventricle. *Cerebral abscess of left frontal lobe.* Purulent meningitis. Cyanosis and dyspnea from birth. Appendectomy; six days later headache, temperature 101° F. Right hemiplegia. Death two days later.

B. *In patent foramen ovale. Ventricular septum closed.*

(*a*) *No other anomaly.*

9. *Rostan. Case VII, Thèse de Genève,* 1884. Male, aged sixty-five years. Large patent foramen ovale. Thrombosis of right auricle. *Multiple areas of cerebral softening.* (*a*) In third frontal combination. (*b*) Cicatrized area on anterior surface of left lateral ventricle. No clinical data.

10. *Rostan.* Case X., *Ibid.* Female, aged fifty-four years. Thrombosis in right auricle, *embolism of right Sylvian artery.* Multiple infarcts in lung, spleen and kidneys. Left hemiplegia some days before death. Large patent F. O.
11. *Rostan.* Case XII, *Ibid.* Male, aged twenty-three years. F. O. widely patent. Thrombosis of long saphenous vein. *Multiple infarcts of brain.* (*a*) In left hemisphere. (*b*) In right lenticular nucleus and spleen. No clinical data.
12. *Cohnheim. Allgem. Pathologie,* 1877. *Quoted by Ohm and Rostan.* Adult woman. Thrombosis of veins of legs. Patent F. O. *Recent embolism of Sylvian artery.*
13. *Ohm. Ztschr. f. klin. Med.,* 1907, **61**, 379. Large patent F. O. Thrombosis in hemorrhoidal veins. *Recent embolus in right middle cerebral. Softening in left lenticular nucleus.* Slight cyanosis. Right hemiplegia with facial and hypoglossal paresis and marked dysarthria. Left nasal field of vision defective. Duration one week. Sudden death two weeks later from second cerebral embolus.

(*b*) *Patent F. O. with pulmonary stenosis and closed V. S. (inflammatory type).*

4. *Lallemand. Recherches anat. path. sur l'encephale.* (*Quoted by Ballet*). Patent F. O., tricuspid and pulmonary stenosis; *Cerebral abscess, size of hen's egg in right hemisphere containing 3 ounces of yellowish-green pus* enclosed by thick wall. Brain softened around. Cyanosis and dyspnea from infancy, intense last ten years after menopause. Left hemiplegia twelve days before death. Onset with cramped-like feelings in hand and foot. Reason and speech clear. Localized convulsive twitchings on paralyzed side. Coarse precordial thrill.

Summary. 1. Pulmonary stenosis or atresia with closed interventricular septum is of unusual occurrence and is due to a fetal endocarditis setting in after the heart has formed. Narrowing of the pulmonary tract with associated ventricular septal defect is the much more frequent finding and is due to arrested development in early embryonic life and is usually associated with a deviation to the right of the aorta.

2. In pulmonary atresia the degree of cyanosis is naturally more intense and the duration of life shorter than in pulmonary stenosis. In atresia, however, an associated septal defect facilitates aëration of the blood, especially with a deviation to the right of the aorta; such cases have, therefore, a better prognosis and present a more

moderate degree of cyanosis than does pulmonary atresia with closed interventricular septum. In pulmonary stenosis, on the other hand, an associated septal defect is *unfavorable*, for it tends both to reduce the volume of blood passing through the stenosed orifice and to permit the passage of venous blood into the arterial stream. The most favorable prognosis, therefore, in pulmonary stenosis, is in cases where the ventricular septum is closed.

3. Dyspneic attacks are especially frequent and severe in cases where a marked ischemia of the pulmonary circulation is present, as in pulmonary stenosis with pinhead orifice and closed septum and in certain cases of patent ductus arteriosus.

4. Cerebral complications of the nature of abscess or infarction are a frequent complication of congenital cardiac cases presenting defects in the interauricular or ventricular septum, and are in the great majority of cases embolic in origin, from a focus in the venous system (paradoxical or crossed embolism). Two cases of this interesting finding are here added to the literature.

5. Anatomical conclusions on the associated ventricular septal defect and deviation to the right of aorta in Cases II and III.

(*a*) In cases of "Rechtslage" of the aorta the position of the pars membranacea septi is altered in relation to the aortic cusps but is not changed in regard to the right auricle and ventricle.

(*b*) If the defect in the interventricular septum is situated posteriorly just in front of the pars membranacea septi it will open into the sinus of the right ventricle directly under the tricuspid segment, and if "Rechtslage" of the aorta be present, this vessel will appear to arise from the sinus also; while, if the defect be situated more anteriorly, it will open into the conus of the ventricle from which again the aorta will appear to arise.

(*c*) In pulmonary stenosis or atresia with septal defect, the condition of the conus of the right ventricle, whether hypoplastic or not, will depend on whether the defect in the septum opens into the sinus of the ventricle or into the conus; in the former case the conus will be small and aplastic; in the latter it will be large and thick-walled.

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CLINICAL OBSERVATIONS ON HEART BLOCK.* †

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AND
Louis E. Viko,
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Occasionally there appears in the clinic a patient with heart block and as such he is examined with a good deal of passing interest. A few striking cases influence greatly our impressions of the incidence, causes, complications and prognosis of the condition. Further study and years of observation may not justify all these first impressions. To obtain more accurate data on heart block we have made a study of all of such cases electrocardiographed in our laboratory at the Massachusetts General Hospital in the past seven and a half years. Without the use of the electrocardiograph the all-important cases of intraventricular block would be missed, as well as certain points of which we shall speak concerning auriculo-ventricular block. From the standpoint of general interest we shall also include the few cases of so-called sino-auricular block that we have seen. Post-mortem examinations have not been carried out in a sufficient number of cases to warrant detailed report in this group.

At the outset it is necessary to define briefly the types of heart block:

Complete auriculo-ventricular block consists of complete dissociation between auricular and ventricular contractions not due to excessive irritability of the ventricular pacemaker. Thus it is

* From the Medical Clinic and Cardiographic Laboratory of the Massachusetts General Hospital.

† Read before the Association of American Physicians, Washington, May 3, 1922.

necessary to distinguish between complete heart block and complete auriculo-ventricular dissociation. We have considered an idio-ventricular rate of 60 as the borderline.

Partial auriculo-ventricular block consists of partial dissociation between auricular and ventricular activity in which the conduction time, as expressed electrocardiographically by the *P-R* interval, is abnormally long or in which there are dropped beats, and where ventricular escape is not primarily the cause of the dissociation. For the sake of clearness we have added to this series only those cases with dropped beats or with a *P-R* interval of 0.2 second or over. The borderline group with *P-R* intervals ranging from 0.18 up to 0.20 second we have omitted here, so that there may not be the least question as to the presence of partial block.

Intraventricular block is the expression used for delay or blocking in the arborizations of the auriculo-ventricular conduction system below the bifurcation of the bundle of His. The greater degree is considered to be high-grade block in one of the two main branches of the bundle, which supply left and right ventricles respectively. Such lesions give characteristic electrocardiograms.

Lesser grades of intraventricular block—produced by partial blocking in the main branches of the auriculo-ventricular bundle, or by extensive lesions in the finer arborizations or by both, are also determined electrocardiographically by deformity of the ventricular complexes. In this series only well marked cases have been included. Cases of doubtful aberration have been omitted though without question there is a fairly wide border-line between normal and abnormal electrocardiograms.

Finally "sino-auricular" block is the term generally applied to that condition of the cardiac mechanism in which the sino-auricular node itself fails to function, either at intervals, giving rise to pauses of the whole heart about equal to the interval between two normal beats, or with a distinct halving of the rate of the sino-auricular pacemaker, or with a very slow regular sino-auricular rhythm, or with auricular standstill and idio-ventricular rhythm.

The following table shows the frequency of the various types of heart block found among 3219 cases electrocardiographed at the Massachusetts General Hospital from October 21, 1914, to March 15, 1922. 6719 plates were taken.

TABLE I.

Type of block.	Cases.	Per cent.
Auriculo-ventricular block	156	4.8
Complete	27	0.8
Partial	129	4.0
Intraventricular block	130	4.0
Bundle Branch	41	1.2
Lesser degrees ("aberration")	89	2.8
All cases showing auriculo-ventricular or intraventricular block	252	7.8
"Sino-auricular block"	11	0.3

Complete auriculo-ventricular block we have found 19 times in the male and 8 times in the female. The extremes in age in our series were six years and eighty-three years, but there were only 4 cases under forty years of age. The probable etiological factors were arteriosclerosis in 15 cases, or 56 per cent of the total, syphilis in 4 cases, diphtheria in 3 cases, rheumatic fever in 2 cases and doubtful in 3 cases. Digitalis may have been something of a factor in but 2 cases. Heart failure was found in only 6 cases at the time of the first record of the presence of complete heart block; 3 of these were of the anginal type and 3 of the congestive. Stokes-Adams attacks occurred in only 6 cases, or 22 per cent. The ventricular rates ranged from 25 to the minute up to 60, being in the thirties in 13 cases. Electrocardiograms showed intraventricular block in addi-

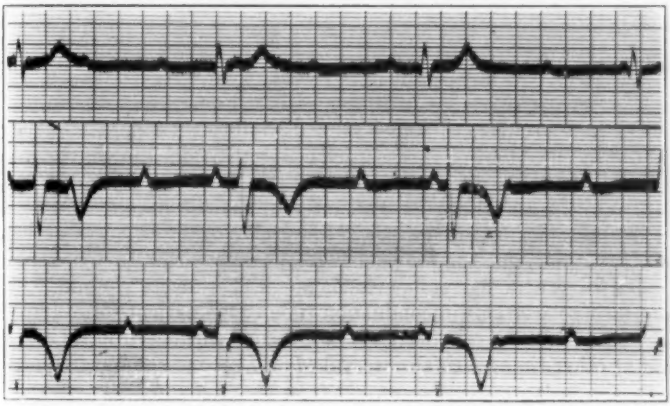

FIG. 1.—Electrocardiogram of S., showing complete auriculo-ventricular block and intraventricular block ("aberration") in addition. Leads I, II and III. In this and in the following figures abscissæ mark the time in 0.2 second intervals and ordinates mark the amplitude in 10^{-4} volts.

tion to complete auriculo-ventricular block in 15 of the patients, or 56 per cent (Fig. 1). Of these 3 showed well-marked bundle branch block. Auricular fibrillation occurred in 2 instances. Of 24 cases followed, 20 of them right up to date, 12 have died from heart failure, 7 of them within one year of the discovery of the complete heart block. Nine cases were "well" or in "fair condition," though still showing heart block when last noted, from one to seven years after the first record of the complete block. Of these 9, 5 had survived over five years, 4 of them being the 4 cases under forty years of age and 3 of these probably diphtheritic in origin. The fifth case was a man about fifty years of age with well treated syphilis.

Of the 129 cases of *partial auriculo-ventricular block*, 91 were male and 38 female. The age limits observed were birth and seventy-

nine years. Sixty-two, or 48 per cent, were under forty years. The etiology of the heart disease in the group included rheumatic fever in 57 cases, arteriosclerosis in 34, syphilis in 12, doubtful in 5, miscellaneous (including one congenital block case) in 12, and no heart disease in 9. Digitalis was apparently chiefly responsible for the partial block in 65 cases, or 50.4 per cent, as shown by the characteristic flattening or inversion of the *T* wave of the electrocardiogram (compare Figs. 2 and 3), by the amount of digitalis given and

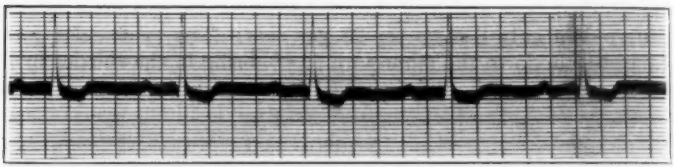

FIG. 2.—Electrocardiogram of C., showing partial auriculo-ventricular block of digitalis origin. Note the long P–R interval and the inverted T wave. Lead II.

by the recovery from the block after digitalis was stopped. Angina pectoris occurred in only 4 cases, and congestive failure in 49. Stokes-Adams attacks were found to have occurred in only 4 cases. The electrocardiogram showed a *P-R* interval varying from 0.20 second to 0.59 second. There was 1 case showing possibly a *P-R* interval of 0.85 second; this is more likely explained, however, by a dropped beat with ventricular escape following. There were a number of interesting variations in conduction time. One patient for example showed a *P-R* interval at times of 0.32 second without dropped beats and at other times with an interval of 0.17 second showed frequent

FIG. 3.—Electrocardiogram of M., showing partial auriculo-ventricular block not of digitalis origin. Note the long P–R interval and the upright T wave. Lead II.

dropped beats without any progressive lengthening of the interval. Another patient showed at one time a high grade partial block, with two or three to one rhythm, and on repeated examinations at other times normal rhythm and a *P-R* interval of 0.16 to 0.18 second. The cause of the paroxysm of heart block in this case was not found out, though there was undoubtedly an arteriosclerotic background, for the man had angina pectoris also. Intraventricular block was found in 19 cases of the whole group, or 15 per cent, being of the

bundle branch type in 11 cases. Auricular fibrillation was present in 9 cases, in fact all those cases of auricular fibrillation with a ventricular rate of 45 or less being arbitrarily added to the group, but not including 2 cases with the regular idio-ventricular rhythm of complete heart block. Of these 9 cases of auricular fibrillation, 8 showed a well marked digitalization of the *T* wave. Seventy-eight of the 129 patients showing partial auriculo-ventricular block have been followed to date; 47 have had cardiac deaths and 21 are now in fair or good health.

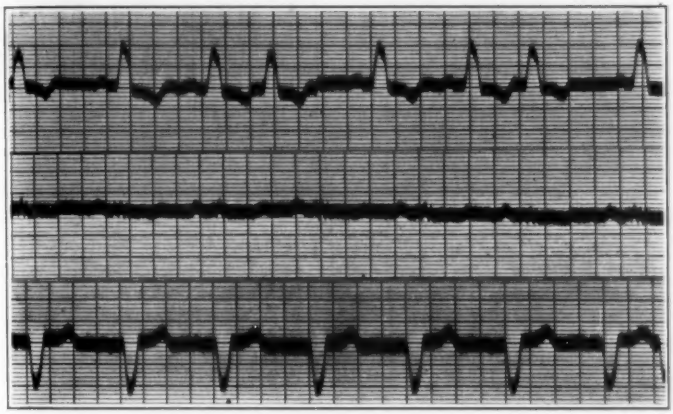

FIG. 4.—Electrocardiogram of Ga., showing intraventricular block of the right bundle branch type. Leads I, II and III.

Intraventricular block of the bundle branch type (Figs. 4 and 5), found in 41 cases of the 3219 electrocardiographed, occurred 34 times in the male and 7 times in the female. All but 2 cases were over forty years of age, the average being sixty years, the highest of all the groups. The youngest case was twenty-nine years of age and resulted temporarily from quinidine. Arteriosclerosis was apparently responsible in 33 of the patients, or 80.1 per cent, rheumatic fever in 4 cases, and syphilis in 3 cases. Although many of the patients received digitalis for congestive failure no relationship could be found which in this group would indicate that digitalis was in any way responsible for the intraventricular block. In 2 cases transient bundle branch block was produced by quinidine sulphate and in 2 other cases there was no change in the block when quinidine was administered. Angina pectoris occurred in 8 cases and congestive failure in 23. Stokes-Adams attacks occurred in 2 cases, one of which had also partial auriculo-ventricular block. Hypertension was found in 24 cases, or well over half. Auriculo-ventricular block occurred in 14 of the 41 patients, complete in 2

and partial in 12. Auricular fibrillation was found in 7 cases, and auricular paroxysmal tachycardia in 2. The block was of the right branch type in 40 cases and of the left branch type in only 1 case.* Of 36 cases followed to date 26 have died, 22 of cardiac failure, 13 of them within one year and 10 within six months of the discovery of the block.

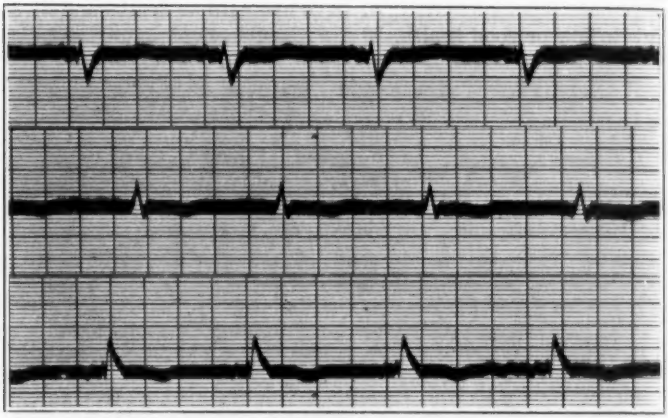

FIG. 5.—Electrocardiogram of Go., showing intraventricular block of the left bundle branch type. Leads I, II and III. (Previously published in the Medical Clinics of North America, January, 1920, **3**, 1035.)

Lesser degrees of intraventricular block (Fig. 6) have been found in 89 cases, 57 male and 32 female. The age limits were twelve and eighty-two years in the group, 17 of the patients being under forty years of age. Arteriosclerosis was apparently responsible in 53 cases, or 59 per cent, rheumatic fever in 22 cases and syphilis in 7. Digitalis did not appear to be a significant factor in any of our cases although it was frequently given because of the presence of heart failure. Quinidine sulphate was the cause of transient aberration in 4 cases, not including the 2 cases of bundle branch block so produced. Congestive failure occurred in 37 patients, at the time of the discovery of the intraventricular block, and angina pectoris in 15 cases. Auriculo-ventricular block coëxisted in 20 of the patients, complete in 12 and partial in 8. Auricular fibrillation coëxisted in 15 cases. Of 69 cases followed to date, 43 have died from heart failure, 25 of them (or 36 per cent of the total number followed) within six months of the discovery of the block.

* During the past year, up to March 23, 1923, 10 more cases have been discovered at the Massachusetts General Hospital in 514 patients electrocardiographed, 8 of the right bundle branch and 2 of the left bundle branch.

"*Sino-auricular block*" was found in 11 cases, 7 male and 4 female. The age limits were seven and seventy-nine years, the majority of the patients being below forty years of age. There was no heart disease in 7 cases, while of the other 4, arteriosclerotic heart disease was present in 2, rheumatic in 1 and hypertensive in 1. Digitalis was primarily responsible in 6 cases, including the 4 with heart disease. There were no Stokes-Adams attacks in this group. In 5 patients the block was complete, giving rise to auricular standstill, in 4 cases there were "dropped beats," in 1 case a very slow regular sino-auricular rhythm of 38, and in 1 case the sino-auricular rate suddenly halved after exercise. The *P-R* intervals when present were within normal limits. The condition was transient in all cases, without effect on life.

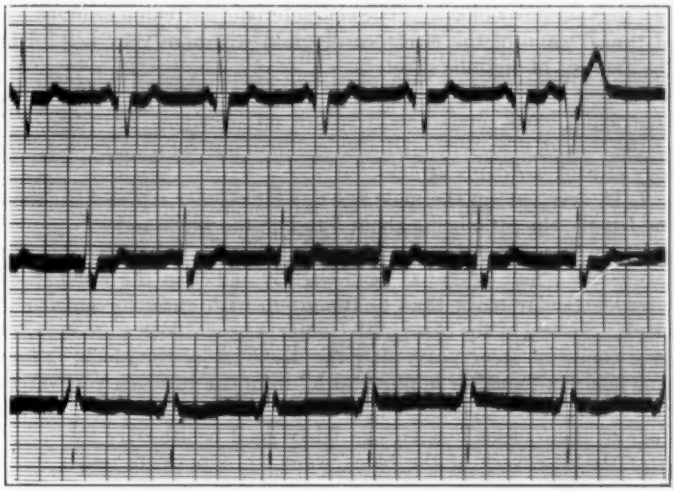

FIG. 6.—Electrocardiogram of W., showing a lesser grade of intraventricular block ("aberration"). Note the wide S$_{II}$. Leads I, II, and III.

Conclusions. 1. Intraventricular block is almost as frequently seen in a large medical clinic as is auriculo-ventricular block, 4.0 per cent having been found in 3219 cases observed at the Massachusetts General Hospital, as compared with 4.8 per cent of the latter type.

2. Complete auriculo-ventricular block in our series showed one-fifth the frequency of unquestionable partial auriculo-ventricular block.

3. Bundle branch block of high grade made up slightly less than one-third of our total number of cases of intraventricular block.

4. Sino-auricular block was rarely found, less than half as often as complete auriculo-ventricular heart block.

5. Arteriosclerosis was apparently responsible for the majority of our cases of complete auriculo-ventricular block and of intraventricular block of all degrees, but especially of bundle branch type, where it figured as the chief factor in over 80 per cent.

6. In our series syphilis was a probable factor in 16 of 156 cases of auriculo-ventricular block and in 11 of 130 cases of intraventricular block. Antiluetic treatment in a number of these cases which have been followed has not abolished the block, although disappearance of heart block under treatment has been reported and we have seen one such probable case in France during the war.

7. In the series of partial auriculo-ventricular block digitalis seemed to be chiefly responsible in more than half, on a background of rheumatic heart disease more often than arteriosclerotic heart disease. Digitalis was also largely responsible for 6 of the 11 cases of "sino-auricular block." The characteristic flattening or inversion of the *T* wave of the electrocardiogram was here very helpful in the analysis of digitalis effect.

8. Less than one-quarter of the cases of complete auriculo-ventricular block showed heart failure, either anginal or congestive, at the time of discovery, and also less than one quarter gave a history of Stokes-Adams attacks.

9. In every group the male sex was far oftener represented than the female, the ratio being about 5 to 2 in the whole series.

10. In our series the mortality from heart failure in the last seven and a half years has been slightly higher in the group with intraventricular block than in the group with auriculo-ventricular block. Several of the cases with complete heart block were in fairly good condition some years after the discovery of the block, in fact nine being in "good or in fair health" from one to seven years after the first electrocardiographic evidence of complete heart block. Four of the 5 cases surviving in fairly good health over five years after the discovery of the block were the 4 patients under forty years of age.

11. Heart failure was found more often in the patients with intraventricular block than in those with auriculo-ventricular block, especially heart failure of the anginal type. Angina pectoris was found about four times more often in intraventricular block than in auriculo-ventricular block.

12. It appears from this study that intraventricular block is of greater significance than auriculo-ventricular block. For its detection the electrocardiograph is essential.

BLOOD-PRESSURE REACTIONS TO PASSIVE POSTURAL CHANGES AN INDEX TO MYOCARDIAL EFFICIENCY.

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Experiences during the World War served to emphasize in the minds of the medical profession the importance of the cardiac group of diseases, and the necessity for early recognition of myocardial inefficiency. Previously we exhausted our efforts in trying to make fine diagnoses of the various valvular lesions, and, as a result, often pronounced a heart normal because of absence of murmurs and overlooked a bad myocardium. A proper conception of the efficiency of the myocardium is perhaps the most important function of the cardiologist or the general practitioner. To recognize the heart as a muscle and to be able to evaluate its capacity is a most important art in order to institute proper treatment as well as to make a prognosis. The best of judgment is often put to a test in differentiating between functional and organic disease, whether valvular or myocardial.

Because of these difficulties many tests have been devised to determine myocardial efficiency, the exercise test being the most popular. The interpretation of these tests is based on the response of the pulse rate or blood-pressure to exercise, and the ability of the heart to resume the normal in a given length of time. Most recently the vital capacity of the lungs has been recommended as an index to cardiac efficiency. Our experience in using these tests in a series of cardiac cases resulted in waning enthusiasm because of too much elasticity in their performance. The various exercise tests do not mean the same amount of work for each individual because of variations in dexterity in their performance, and, consequently, the cardiac reaction may easily be misinterpreted. The vital capacity test is also of doubtful value because of the various conditions that have to be eliminated before we are justified in interpreting a deficient vital capacity of the lungs as an evidence of an impaired myocardium.

More than three years ago I became interested in the study of the effect of postural changes in blood-pressure as an index to vasomotor tone. Crampton calls attention to changes in blood-pressure with change of posture and interprets these as evidence of vasomotor status, especially as related to the splanchnic vessels. In his empirical table he refers only to the systolic pressure and pulse rate as the index. I soon became convinced that change in systolic pressure could not be due to vasomotor tone but was, rather, a response of the myocardium to the effect of gravity and to the muscular activity indulged in with changes in posture.

Sewall, in a most excellent article on this subject, states that the relative evaluation of systolic and diastolic blood-pressure leads to the conclusion that the former is an index of cardiac energy expended, a decision in keeping with observations on cardiac strain due to effort. Changes in diastolic pressure with changes of posture are more likely to indicate change in vasomotor tone, and Sewall, in the same article, states that the diastolic blood-pressure is generally admitted to measure the peripheral resistance to the circulation and to be an index of vasomotor tone. In our studies we recognized that even the slight effort of rising from the horizontal to the erect

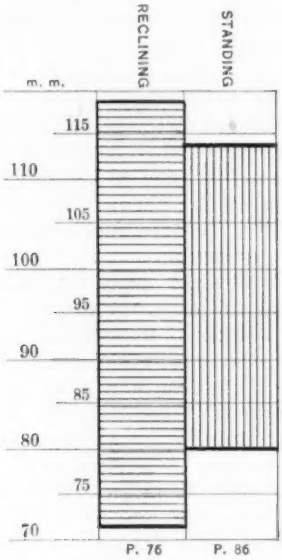

FIG. 1.—The average variation of blood-pressure and pulse rate with passive postural changes in ninety healthy young women.

posture must produce change in systolic pressure, and variation in pulse rate is also to be expected from the same exercise. However, it must be remembered that fundamentally exercise inhibits the vagus and thus tends to slow the pulse rate. In view of these facts, it seemed advisable to continue the study by eliminating the influence of exercise on pressure as well as pulse rate, and for this purpose we devised a tilting table on which a patient could be placed and blood-pressure and pulse rate observations made in both the reclining and the erect posture without effort or anxiety on the part of the patient, and with ease to the observer. An effort was also made to eliminate all possible variation in technic and, con-

sequently, the mercurial sphygmomanometer was used in our observations as well as Bowles' stethoscope with an armband to hold it in position to maintain a uniform pressure on the brachial artery. The readings were made within thirty seconds after placing the patient in the upright position, and the pulse rate was based on quarter minute observations. In this way we limited our study to the influence of gravity on the blood volume, and the effort of the circulatory system to overcome this factor and to maintain a proper circulatory equilibrium.

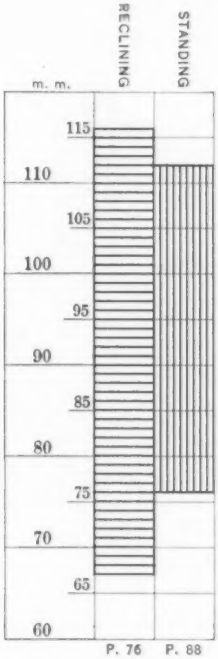

FIG. 2.—Miss M. B., No. 135746. Mitral lesion (tonsillar infections). No symptoms of cardiac inefficiency. Normal responses.

First, an effort was made to find the normal reaction of blood-pressure and pulse rate to this passive postural change in the healthy individual. For this purpose we took 90 young women from our Normal School of Physical Education, who had been in training for some months, and who, on entrance to the school had been carefully examined in order to eliminate all possible cardiac cases. To our surprise we found a marked uniformity in the reactions to passive postural change, fully 80 per cent showing a *slight decrease*

in systolic pressure and a slightly greater rise in diastolic pressure, thus cutting the pulse pressure at both extremes. The pulse rate also increased uniformly, as much or more than in the change of position when assumed actively. In very few cases was the systolic higher in the erect posture and in no case was the diastolic found to

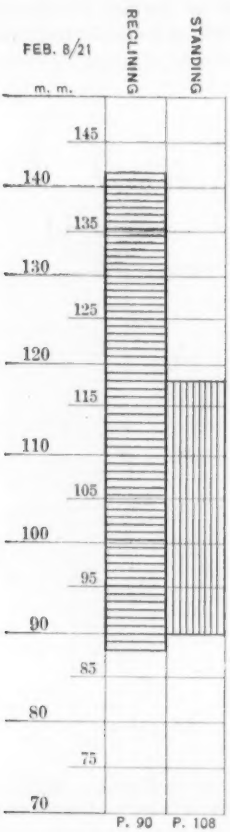

FIG. 3.—J. D. O., No. 136383. Chronic myocarditis. Attacks of acute dilatation associated with alcoholism. Note marked change in pulse pressure.

be lower. The *average maximum pressure in the 90 girls was* 118, *minimum* 72, *pulse rate* 76, as observed in the reclining position. After putting them in the erect posture the *average maximum pressure was found to be* 114, *minimum* 80, *pulse rate* 86. Since this definite series of normals was studied many normal individuals have been observed, both men and women, and with parallel results.

My findings in hundreds of cases have been so uniform that I feel confident that a marked deviation from these figures is an indication of some pathological condition. I have never found anything but very slight increase in systolic pressure when placing the individual in the erect position, and only once a decided drop in diastolic pressure with change of posture, and that individual complained

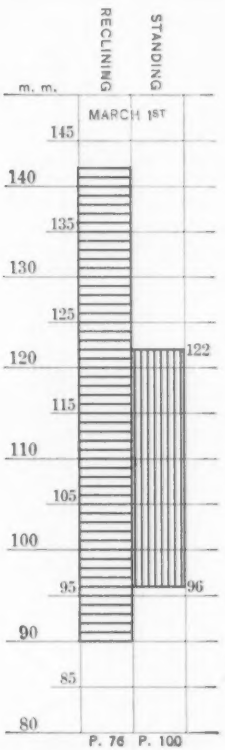

FIG. 4.—Mrs. N., No. 135192. Arteriosclerosis, hypertension, myocarditis with alternating pulse. Symptoms of angina. Note marked drop in systolic pressure with alteration.

of feeling faint and her appearance indicated this, which would tend to prove a sudden loss of vasomotor tone.

After obtaining these findings for the normal a systematic study was made of cases with definite cardio-vascular disease, especially those borderline cases where exercise tests were contraindicated, such as in angina pectoris. We were impressed with the fact that the drop in systolic pressure was definitely greater than in the

normal cases, but the diastolic pressure behaved very much the same as in the normal case or in a few cases remained stationary. The drop in systolic pressure in the various types of cardiac cases studied ranged from 10 to 40 or 50 mm., depending, of course, on the degree of arterial tension, and impairment of the myocardium. I might interpolate that in cases of marked arterial hypertension with symptomatic evidence of myocardial inefficiency the change

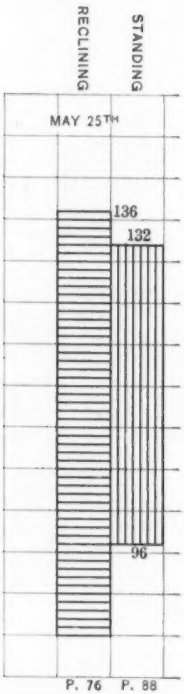

FIG. 5.—Dr. M. T., No. 136988, aged fifty-two years, chronic myocarditis. In college a sprinter and athlete. Symptoms of tachycardia, precordial discomfort with exertion. Note small pulse pressure with pronounced increase in pulse rate. Observation March 1, 1921.

in systolic blood-pressure with change of position was only a few millimeters, so that I feel justified in stating that an efficient myocardium, even in arterial hypertension, maintains the systolic pressure within 8 or 10 mm. of that found in the reclining position. As a result of three years' observation of almost daily use of this test I feel warranted in offering it as a test for estimating the efficiency of the myocardium. Graphic figures are presented showing the changes noted in different types of cases of cardiac disease

with or without symptomatic evidence of cardiac inefficiency. In these studies changes also in pulse rate should always be noted and can be taken as additional evidence of myocardial embarrassment, as in all cases there is a greater increase in rate than would

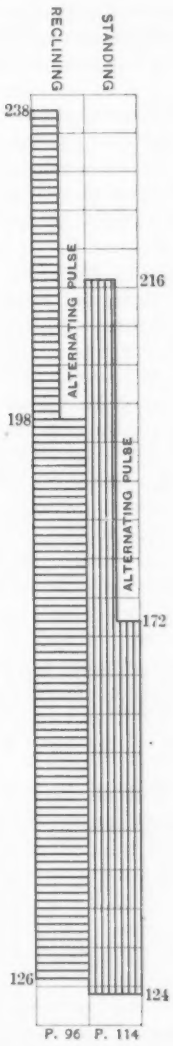

FIG. 6.—Dr. M. T. (same). Observation May 25, 1921, after carrying out program of graduated exercise and digitalis therapy.

be expected in the normal even without effort on the part of the patient in changing positions. Moreover, I have found the test of value when used at intervals to note a definite evidence of improvement while the patient is under treatment, whether this be in the form of digitalis therapy or graduated exercise. In a number of cases we have been impressed with the gradual improvement in the systolic pressure with digitalization indicating a better efficiency of the heart muscle, and in our opinion, corroborating the value of the test.

In a graphic representation of these studies the most striking feature is the decided change in pulse pressure, since with the passive postural change it is curtailed at both extremes, and a small pulse pressure, I believe, is accepted as definite evidence of circulatory inefficiency and might be compared with the so-called secondary low pressure.

Since beginning these studies Max Ellis reports a series of observations in normal individuals and his findings of changes from reclining to erect postures correspond in the main with our results. In our opinion the uniform range in systolic pressure is an indication of the ability of the heart to respond to a sudden demand to maintain the proper distribution of blood, especially to the brain, and the rise in diastolic pressure is the response of the vasomotor system to further help resist the influence of gravity on the distribution of blood. In the great majority of my cases the diastolic pressure was maintained or rose several millimeters, indicating a uniform response of the vasomotor mechanism. Consequently, in all types of heart disease, with or without arterial hypertension, three striking features are manifested with the passive postural changes. First, a decided fall in systolic pressure and a uniform maintenance or rise in diastolic pressure. Second, marked decrease in pulse pressure, which is the most striking evidence of inefficiency of the circulation. Third, the decided increase in pulse rate which, in spite of the absence of muscular effort, is further evidence of a decided effort on the part of the heart to maintain a circulatory equilibrium.

In performing the test it is necessary to have a tilting table so constructed that the patient can be changed from the horizontal to the erect posture without great effort on the part of the observer and without anxiety to the patient, and the mechanism for manipulating the table should be such that the change of posture can be made within a few seconds. Our table operates with a crank and is steadied by springs in the pulley chain so as to avoid jarring or sudden jerking of the patient.

Summary. 1. Very little has been recorded in literature relative to passive postural change of the blood-pressure in the normal individual, and none, as far as I have been able to determine, relative to these changes in heart disease.

2. A drop of more than 6 to 8 per cent in the systolic pressure, in changing from the reclining to the erect posture, may be viewed as an evidence of myocardial inefficiency. Careful history and physical examination will usually add support to this conclusion.

3. The rise in diastolic pressure is an index to the response of vasomotor mechanism to assist the heart to maintain circulatory equilibrium against the influence of gravity.

4. Pulse rate increase with change of position is greater than that noted with active postural change, indicating increased effort on the part of the heart to work against the influence of gravity.

5. This test is applicable in cases of angina pectoris or advanced arteriosclerosis where exercise tests are contraindicated. Cases of angina pectoris uniformly show a decided drop in systolic pressure.

6. The test is uniform for all individuals as it practically eliminates all but the factor of gravity in the circulation. It is easily applied without discomfort to the patient and can be used at intervals for the purpose of noting progress in the management of cases and as an index to the influence of digitalis or exercise on myocardial efficiency.

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A CONSIDERATION OF THE VARIOUS LAWS OF HEREDITY AND THEIR APPLICATION TO CONDITIONS IN MAN.*

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Heredity is a science devoted to the study of the phenomena of breeding.

The mechanism of heredity came into play with the appearance of bisexual life on the surface of the earth. Its laws will continue to function until such life becomes extinct. The efforts of ancient, of medieval, and of modern investigators, to unravel the workings of the mechanism of heredity, form an interesting chapter in the development of biological knowledge.[12]

* Submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine, March, 1922.

The physico-biological characters, which are transmitted to subsequent generations by means of the germ plasm, furnish the concrete evidences for studies in heredity. A biological character signifies a type of physical and chemical composition possessed by individuals, by which they may be differentiated. Characters are rendered physically immortal by heredity, and the study of heredity becomes, in consequence, an investigation of the mechanism of physical immortality. The vehicles on which the transmission of the characters depends are the nuclear structures, chromosomes in all germ cells, and in certain instances the cytoplasm of the germ cells. The hereditary substances in the chromosomes and cytoplastic substances together comprise the germ plasm. The germ cells or gametes in man are the ova and the spermatozoa.

Heredity never deals with the etiological factors of disease. Any characters appearing in man that can be proved hereditary are normal, biologically speaking, regardless of how the characters may unfit their bearer for harmonious coöperation in the economical and social programs of civilization. This conception becomes clear when it is remembered that characters are brought to their bearer as an integral part of the stuff from which he developed, and that there is no alteration from the normal course of life. The factor on which the character depends is in the germ plasm. The character undergoes development along a fairly fixed line, as a component part of the body in which it appears. Hereditary characters in all plants and animals, and even in man in certain instances, are considered as expressions of normal features. The characters in man which embarrass his participation in all or certain parts of his duties and pleasures are looked on as expressions of disease. A man with an untoward hereditary character cannot be otherwise from a biological and physiological standpoint. The embarrassing characters are the physical expression of the type of stuff of which he is composed genetically, and not the expression of pathological processes.

By heredity the quantitative and qualitative characters in all bisexual species are kept extant and limited. Under similar conditions of reproduction, the numerical expression of the transmission of these characters follows very closely, or is reducible to, a fairly definite ratio. A character once proved hereditary is always hereditary, and not hereditary on a percentage basis.

The science of heredity includes the study of the intermediate as well as of the immediate stage of certain features of the life cycle. The ova and spermatozoa form the intermediate stage of the life cycle in man. The rearrangement of chromosomes which occurs following their union furnishes the fundamental basis for the study of the method of production of the tangible evidences of heredity in the immediate stage, the corporal stage, of the life cycle.

It is remarkable that heredity, a science so familiar not only to

physicians, but to all reading men, whose principles are so easily gathered from the works of biologists, should be characterized by a lack of accuracy in medical literature.

Heredity as ordinarily used by medical writers means the presence of a like condition in parent and child. This occurrence is usually described as one of the etiological factors for the disease under consideration. The laws of heredity which have been established are at variance with this usage.

Kölreuter[23] made the first systematic investigation of hybridization, which is the first stage resulting from the crossing of parents with different inheritable characters. By his experiments he established the fact that the hybrid offspring generally looks as like the male as the female parent.

Mendel[29] carried the work of Kölreuter one step farther by mating hybrid with hybrid. When the products of this mating were examined, he found that the parental characters which entered into the formation of the hybrid were separated in a peculiarly striking manner, and that the hybrid reappeared in its identical form. To this phenomenon Mendel applied the phrase. "segregation of characters." This is now known as the first law of heredity. Mendel believed that in the offspring of a mating all characters are segregated independently, and that there is no interrelationship in the transmission of characters. This belief is usually spoken of as the "independent assortment of characters," and is the second law of Mendel and of the science of heredity. This law has been found to be only partially true.

Since the time of Mendel four other laws have been derived from experiments carried out on plants and animals. They are known as: (1) Linkage, and its corollary, crossing over; (2) linear order of genes; (3) interference, and (4) limitation of the linkage groups. They have been carefully studied by Morgan.[30] Linkage of characters has been found to occur in man. The corollary and the other three laws have not yet been worked out in man.

The discovery of the spermatozoön in man by Leeuwenhoek,[24] the ovum in mammals by von Baer,[5] the cell by Schleiden and Schwann,[41, 42] the chromosomes by van Beneden,[4] the theory of cellular continuity by Virchow,[44] the theory of germinal continuity by Nussbaum,[34] furnished the material on which Weismann[46] evolved the theory of the germ plasm. This theory clearly isolated the ultimate units on which physico-biological characters must depend. The theoretic units are located in the germ plasm, and in their finest division are known as "biophors;" aggregations of biophors are known as "determiners," and the latter when grouped together are known as "ids." Groups of ids are called "idants," which are identical with chromosomes. Determiners are the fundamental aggregations of hereditary units in the germ plasm. Weismann vivified the significance of the spermatozoön and ovum with their

nuclear and cytoplastic structures as the medium for the transmission of the ultimate units of hereditary characters.

The terminology used in studies in heredity is very simple. The parental generation, or the stock from which a series of studies has been made, is expressed by the symbol, *P*. The first product resulting from a mating of the parental generation in which unlike characters are crossed is known as the hybrid, and this stage is spoken of as the first filial generation. By mating members of the first filial generation, the second filial generation is obtained. This generation was the important one in the studies of Mendel. All generations, except the parental, are designated by the letter *F*, and a subnumeral which indicates the generation under consideration. The term homozygote is used to designate individuals who are pure bred for a particular character. The homozygote. when crossed with a homozygote with like characters, always breeds true to the characters present. The term heterozygote refers to an individual who, while possessing a certain character in his somatic cells, because of certain properties in the germinal cells, has the ability of transmitting not only a character present in the somatic cells but a character which is concealed or dormant in the germinal cells. The determiners for the dormant and evident characters are located in the germ plasm.

The discovery of the heterozygous property of plants was one of the most fundamental discoveries made by Mendel. In man the heterozygous person can be determined only by breeding, whereas in plants the knowledge of the nature of the parental generation furnishes information which enables an observer of plant breeding to determine, in certain instances, by physical inspection the homozygous and heterozygous types.

The property of the hybrid in plants to conceal one character while another was evident led Mendel to introduce the words "dominant" and "recessive." The character which is visibly represented in the hybrid is spoken of as dominant, while the other is spoken of as recessive. These words have been used in connection with the study of heredity in man, but erroneously so, as there is no direct way of determining which of the two characters will be dominant, because when two persons are mated to produce a cross of different characters, instead of a hybrid generation, there is an immediate progression to the segregation of the characters introduced in the cross with the production of both homozygous and heterozygous individuals, just as occurs in plants and fowls in the second filial generation. The first filial generation, or hybrid stage, in man is absent. The terms "dormant" and "evident" are more expressive when speaking of hereditary characters in man.

Mendel left no graphic illustration of his work which was carried out on species and subspecies of the edible pea (Pisum sativium) and species of the hawkweed (Hieracium) but Correns,[14] who dis-

covered Mendel's work, confirmed and extended it, and visualized the parental generation, the first filial generation, and the second filial generation during which the segregation of characters took place (Fig. 1). In this experiment the four o'clock was used. A red flower (character red) was crossed with a white flower (character white). The result was a pink hybrid. When two of the hybrids were mated together, their offspring consisted of one red flower, one white, and two pink flowers, commonly spoken of as heterozygotes. The separating was the clearest possible example of what Mendel meant by the expression, "segregation of characters." The red and white if crossed with red and white respectively breed only red and

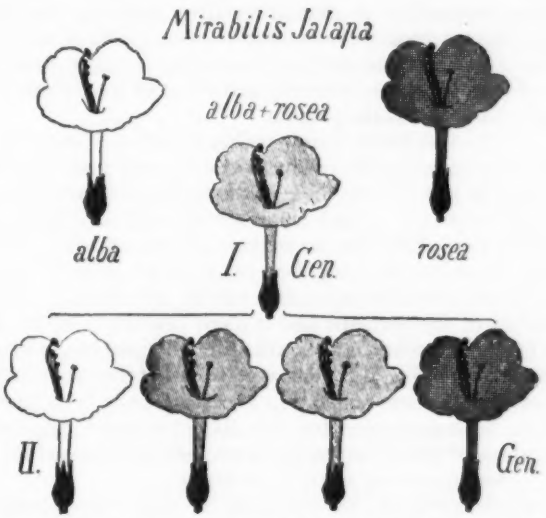


FIG. 1.—A diagram to show inheritance of flower color in crosses of Mirabilis, the "four-o'clock." *Alba*, white parent; *rosea*, red parent; *alba-rosea*, the unfixable F_1 heterozygote of intermediate color, pink. First generation = F_1. Second generation = F_2. (After Correns).

white respectively, whereas if the pink flowers of the second filial generation are crossed with pink flowers the segregation of characters repeats itself.

By a statistical investigation of many crosses Mendel established the now famous 3 to 1 ratio which is approximate and not absolute, as shown by his investigations. He found in Experiment 1, a ratio of 2.96 to 1; in Experiment 2, 3.01 to 1; in Experiment 3, 3.15 to 1; in Experiment 4, 2.95 to 1; in Experiment 5, 2.82 to 1; in Experiment 6, 3.14 to 1; and in Experiment 7, 2.84 to 1. These figures show a rather narrow range of possibilities.

In the study of heredity in man, the absence of the hybrid stage

presents distinct obstacles to the direct application of the scheme used by Mendel in his investigations. The heterozygote in man is identical genetically with the hybrid of plants. Mendel demonstrated the segregation of characters by mating hybrids, which were the offspring of the same parents. The only similar biological and genetic situation in man would be the crossing of sister and brother heterozygotes, provided their heterozygous nature could be proved beforehand. Such a cross in man is clearly impossible. Furthermore, it is quite impossible to say in advance of a mating, whether or not a cross is of heterozygotes, or of homozygotes and heterozygotes. The evident character is always discernible, but the dormant character in man exists without any evidence. It is also often impossible to determine after studying the offspring resulting from a cross between two persons whether the parental generation was heterozygous or homozygous. The homozygous nature of both parents is demonstrated when all the children possess the same characters as the parents.

These difficulties make it impossible to derive Mendelian ratios directly by tabulating the products of crosses in man. Through a long period of time, it may be possible to demonstrate which characters may appear in certain combinations only as evident or dormant characters. Hitherto, no attempt has been made to prove this essential possibility in man, but by such an indirect procedure dominant and recessive characters can be determined. After the relationship of the dormant and evident characters in the heterozygote has been worked out, it will still be impossible to determine in advance of mating the homozygous or heterozygous nature of any particular person, unless his ancestors have been previously proved to be homozygous for the character under consideration. The accuracy of Mendelian ratios in man will be lessened for a long time to come on account of these obstacles.

Certain requirements are necessary in order to determine if a character or condition in man is hereditary and to establish its relationship to another character. The character must be arbitrarily defined, and a contrasted character must be selected. When two characters are crossed, at least three, and preferably four or more, children must result in order to observe the segregation of the characters and to establish their numerical relationships. A cross in man where only two characters are concerned needs investigation through but two generations. The evident characters will be discernible, but the recipients of the dormant characters cannot be distinguished. This fact must be borne in mind constantly, for heterozygous mates will reproduce their ancestors; unless this faculty is recalled, many conditions will be considered hereditary on a percentage basis or else not considered hereditary at all. The heterozygous principle has been responsible for immeasurable misunderstandings in the study of heredity in man. In cases in

which three or four characters are under investigation the four grandparents, the parents, and a final generation of preferably four or more children must be studied; a final generation of less than three children furnishes data of no conclusive value. The *sine qua non* of a hereditary investigation is the knowledge of the characters represented in the germ plasm of the ancestors of the individuals under consideration.

THE INHERITANCE OF THE BLOOD GROUP: STUDY I. In 1900, Shattock[43] observed that the serum of patients suffering from certain diseases agglutinated the red blood cells of healthy men. He also noted the persistence of the agglutinative phenomena during the convalescence from the diseases. In 1901, Landsteiner[24] discovered that the red blood cells of healthy men, because of certain agglutinative properties of the serum, could be classified into three groups. A fourth blood group, Group 1 of the Moss classification, was dis-

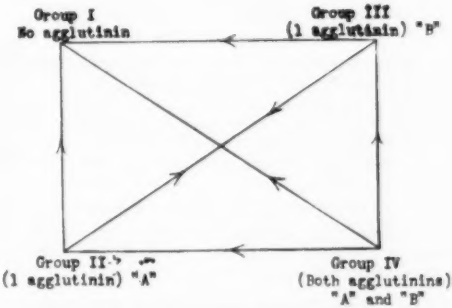


FIG. 2.—The corpuscles of the various groups are agglutinated by the serums of the groups from which the arrows lead. (After Sanford.)

covered by Decastello and Sturli in 1902.[16] In 1907, Jansky[22] made independent observations and reported the existence of four blood groups. The observations were reported independently by Moss[31] in the United States in 1909. The four blood groups known today are arbitrarily designated as Group I, Group II, Group III, and Group IV. They have been classified by Jansky and by Moss. Their classifications differ in that Jansky's Group I is the Group IV of Moss and *vice versa*. The scheme of Moss has been concisely presented by Sanford[40] (Fig. 2). I have followed the Moss classification, although the priority of Jansky is recognized as adopted by the American Association of Immunologists, the Society of American Bacteriologists, and the Association of Pathologists and Bacteriologists.*

The Mendelian transmission of blood group to subsequent generations by the germ cells has been suspected;[37] some definite evidence

* Article on Isohemagglutination: Jour. Am. Med. Assn., 1921, **76**, 130.

has been presented, but certain difficulties remain. This study was made in an attempt to obviate these difficulties.

The material studied was obtained in a unique manner. In discussing my desire to add further data concerning the inheritance of blood group with Dr. W. A. Evans, he suggested that a notice (Fig. 3) be inserted in his health column in the *Chicago Tribune*. It appeared on April 26, 1921. The same request subsequently appeared in all the publications of the Tribune Syndicate. Through the kindness of the Eugenics Record Office, the interests of Mr. A. E. Wiggam was aroused, and a similar request appeared in the *Physical Culture Magazine*, August, 1921. The replies to these requests were mailed to me. Each member of the family was mailed a 3 cc glass tube which contained 1 to 2 cc of 2 per cent sodium citrate solution. The tubes were well corked, packed in cotton in an ordinary mailing tube, and sent by first-class mail. At the same time, instructions were followed for collecting blood from a needle stab in the finger,

IT'S A BONA FIDE INQUIRY.

J. B. writes: "I would like to get the names and addresses of a few families in which four grandparents, both parents, and four or more children of the present generation are living and within reach. Will any one knowing of one or more such families write me the facts? The promise is that no improper use of the information will be made. The object is to get light on a question of family resemblance."

DIFFICULT TO DIAGNOSE COMMENT.

I know the person inquiring and the object of the inquiry. If letters are sent to me I will see that they reach J. B. In violation of our rule we are keeping his name and address on file.

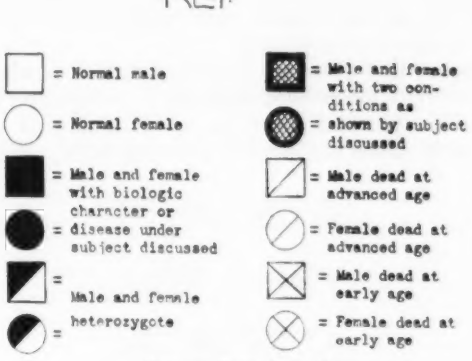
FIG. 3.—Insert from *Chicago Tribune*, April 26, 1921. Kindness of Dr. W. A. Evans.

and for labelling and remailing the tubes. The instructions were accompanied by a letter requesting the coöperation of the family in the work. If the first letter failed, a follow-up letter was sent. One tube was broken; twice hemolysis of the red cells occurred, so that second specimens had to be obtained. The cells were grouped with known Groups II and III serums and checked with homologous serums. Families suitable for this study are very scarce. There is not such a family on record at the Eugenics Record Office, Cold Springs Harbor, New York.*[11]

In 1908, Ottenberg[37] first suspected that the blood group was hereditary and transmitted to subsequent generations according to the laws of Mendel. In 1910, von Dungern and Hirschfeld[18] reported 72 families (348 persons) in which the grouping of the blood had been carried through two generations. They concluded

* I owe my thanks to Mr. E. C. Myers and Dr. J. I. Mershon, Mt. Carroll, Illinois, Dr. H. B. Cole and Dr. B. P. Flinn, Redwood Falls, Minnesota, Dr. R. A. Jacobson and Dr. C. F. Crow, Exira, Iowa, Dr. Greenleaf, Atlantic, Iowa, and Dr. C. C. Bassett, Goodland, Indiana, for their assistance in the work.

that blood group was hereditary and transmitted according to the Mendelian rules. Ottenberg,[38] in 1921, established certain formulas which he considered to be representative of the blood groups. In this study, in contradistinction to Ottenberg's formulas, I have used the terms Group I, Group II, Group III, and Group IV as expressive of a specific biological property of the blood of man. The factor for blood group is considered as comparable to those unexplained factors on which the unit characters height, shape, size, color, etc., in plants and animals depend. The exact formulas of the ultimate units on which hereditary characters depend are unknown.


KEY
= Normal male
= Normal female
= Male and female with biologic character or
= disease under subject discussed
=
Male and female
= heterozygote
= Male and female with two conditions as
= shown by subject discussed
= Male dead at advanced age
= Female dead at advanced age
= Male dead at early age
= Female dead at early age

KEY TO FIGS. 4 TO 41.

If it is assumed as a premise that blood group is expressive of a hereditary character dependent on a unit factor comparable to that for color of flowers, height of plants, etc., it becomes necessary to present data to ascertain if blood group is transmitted

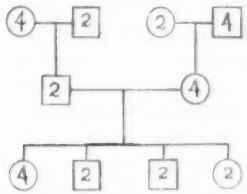


FIG. 4.—Transmission of blood Groups IV and II through three generations.

between generations in a manner similar to that occurring in plants and flowers. The data presented in Fig. 4 consist of the crossing of Group II with Group IV through three generations. If Fig. 4 is compared with Fig. 1 the absence of the hybrid stage or stage of the first filial generation in Fig. 4 will be noted; otherwise a new blood

group having, to a certain extent, the characteristics of both parents would result. In the third generation of the family studied 1 child in Group IV and 3 children in Group II appeared. The blood groups present in the previous generations appeared in the final generation. No other blood groups appeared. If the phenomena observed in the third generation of this family were considered as illustrative of the first law of Mendel, it might be assumed that 2 of the children were homozygous and 2 were heterozygous, as occurs in the Mendelian segregation of characters. It was impossible to demonstrate a basis for the assumption in this family, as it would have been necessary to group the progeny of all 4 children in the family. The result would have been influenced by groups introduced by marriage, and the data obtained might or might not have been of any conclusive value.

The evidence that there are heterozygous individuals for blood group produced by the crossing of Group II and Group IV is shown in Fig. 5. The parental generation on both sides of the family consisted of the union of Group II with Group IV. Both families

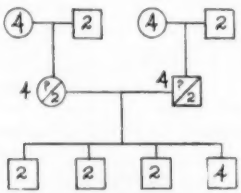


FIG. 5.—Transmission of blood Groups IV and II to the third generation because of the heterozygous nature of one of the parents in the second generation.

had a child in Group II. The mating of these children resulted in 3 children in Group II and 1 child in Group IV. If the blood group is hereditary, the factor for the Group IV must have been present in the germ plasm of either the male or the female parent, for there is no other mechanism in heredity by which it could have appeared in the final generation. A like situation is shown in Fig. 6. The blood of a heterozygote is not different from the blood of a homozygote. The difference is in the germ plasm alone.

The heterozygous property is illustrated in Fig. 6. In the parental generation on the left, the cross consisted of presumably homozygous Group II parents, and on the right a Group IV was crossed with a Group I. The result was a Group II on the left and a Group IV on the right. The final generation showed 2 children in Group II, 1 in Group I, and 1 in Group IV. This happened because of the heterozygous nature of the parental Group IV on the right. Figs. 7 and 8 are also a very clear demonstration that blood group is a distinct hereditary character, as all the characters concerned in the primary generation reappeared in the final genera-

tion. The same phenomenon is observed in Fig. 9, where Groups III and IV appear as the expression of the heterozygous principle.

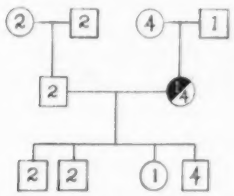


FIG. 6.—The segregation in the third generation of all the characters introduced by the ancestors. The female in the second generation was a heterozygote.

The homozygous nature of blood group is illustrated in Fig. 10. In this family the parental crossings on both sides resulted in children in Group II, which on being crossed produced 4 children in Group II. The same situation is shown in Fig. 5 where Group IV is the

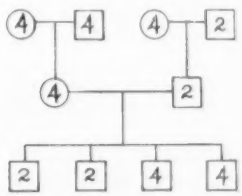


FIG. 7.—Transmission of blood Groups II and IV through three generations. There is no method of demonstrating the homozygous or heterozygous status of the male in the second generation.

homozygous character. Ottenberg,[37] in 1908, demonstrated the homozygous nature of Group III. He reported a father, mother, and 4 children all in Group III. The effect of crossing Groups III and IV is shown in Fig. 11. The homozygous nature of Group I

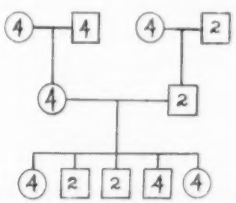


FIG. 8.—Transmission of Groups IV and II through three generations.

has not yet been demonstrated, but it seems reasonable to suppose, from its behavior when crossed with other blood groups, that it

could appear in the homozygous state as well as in the heterozygous state (Figs. 6, 12 and 13).

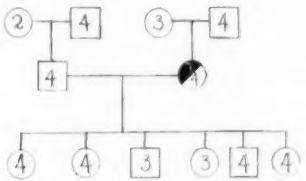


FIG. 9.—Transmission of blood Groups IV and III through three generations by means of a heterozygous female in the second generation.

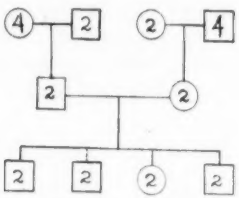


FIG. 10.—Segregation of pure Group II in the second generation as indicated by all the children of the third generation being in Group II.

The expressions, dominant and recessive, are frequently heard in discussing the inheritance of any character. Mendel described

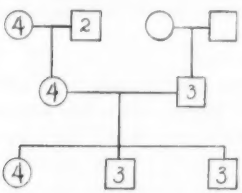


FIG. 11.—Result of crossing pure Groups IV and III through two generations.

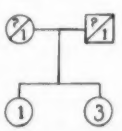


FIG. 12.—The value of the three-generation study for determining the origin of blood group. The Group III is explainable only by information obtained through families as in Fig. 6.

this usage thus: "Those characters which are transmitted entire or almost unchanged in the hybridization and, therefore, in them-

selves constitute the characters of the hybrid, are termed the dominant, and those which become latent in the process, recessive. The expression recessive has been chosen because the characters thereby designated withdraw or entirely disappear in the hybrid, but nevertheless reappear unchanged in their progeny." The hybrid state is absent in all families I have studied, as well as in all the families grouped by von Dungern and Hirschfeld,[18] and by Ottenberg.[39] The absence of the hybrid stage in man is shown in the study of all families reported as illustrative of the transmission of hereditary characters of all kinds, unless the sex linkage phenomenon as seen in hemophilia and in color blindness, may be interpreted as expressive of the hybrid stage. It is, then, improper to use the term dominant and recessive in connection with heredity in man until further studies are made. As the heterozygotes in plants are identical physically and genetically with the plant hybrid, and as the heterozygote in man behaves in the same manner as the heterozygote in plants, it may be possible to work in a reverse manner in order to determine which blood groups in various combinations can appear only as the dormant and evident combinations. If there is no reversal in the relationship of the dormant and evident characters, dominance of one character to another may be spoken of in its true sense. If there is reversal, the use of the expressions, dominant and recessive will remain meaningless. The settlement of this point is, however, not of vital importance in the study of heredity in man; it is more a matter of accuracy and correct usage. It could be of importance, however, in the use of the blood group in the adjudication of medico-legal disputes. Until it is proved which character may appear as dormant in certain unions, the use of blood group in medico-legal affairs will be fraught with great danger, unless the blood grouping is carried in a definite scheme into the preceding generations, and even then the result may be inconclusive (Fig. 18). The possibilities of the medico-legal value of the blood group were mentioned by von Dungern and Hirschfeld in 1910,[18] and by Giraud in 1919.[21]

Ottenberg[38] has presented data in an endeavor to demonstrate the possible blood groups that may result from crossing two persons in the same or different groups. His conclusions were made in conformity with formulas which he had outlined as representative of the various blood groups.

The acceptance by Ottenberg of the hypothesis that in the inheritance of the blood group agglutinogens *A* and *B* of the red cells behaved as dominant characters while the agglutinins, *a* and *b* of the serum behaved as recessive characters is stimulated by the belief that Group IV (Group I of Jansky) can exist only in a pure state (recessive). Ottenberg also believes in the existence in man of a hybrid for blood group, in a variable relationship in the groups of the supposed dominant and recessive characters, and in the union

of *A* and *B* to produce Group IV (*A. B.*) These beliefs are entirely groundless in the light of Mendel's experiments. The dominant and recessive characters are determined by means of the hybrid. A hybrid stage for the blood group is absent in man. Even if Group IV (Group I of Jansky) were a recessive character to one blood group, evidence would have to be presented to establish its relationship to the remaining two groups. My study clearly shows that unions of Group IV (Group I of Jansky) may result in offspring in the other three groups, depending solely on the groups present in previous generations. By crossing a Group II with a Group III it is shown that Group IV (*A, B*) is not the result of the union of *A* and *B*. If a hybrid stage in man existed this result would be possible, and all the children would be in Group IV (*A. B.*). The serum of this hybrid would agglutinate the cells of Groups II and III, and the cells would be agglutinated by the serum of Groups II and III. Such a combination does not exist. Furthermore, if Group IV were to be considered as a hybrid resulting from unions of Groups II and III, crosses of Group IV would always result in children in Groups II, Group IV and Group III. In sufficiently large families the groups would be distributed numerically so as to maintain the relationship of one Group II, two Group IV, and one Group III. Crosses of Group IV may result in only Group IV children. There is no way by which a union of *A* and *B* can explain the origin of Group IV. The conclusions of Moss in reference to the existence of three specific iso-agglutinin combinations, *A, B, C*, in the serum, and three distinct receptor substances *a, b, c*, in the red blood cells, as arranged by that author into four groups comply exactly with data obtained in my study of the germinal transmission of the blood group to subsequent generations. The constitution of each blood group is specific whether present in the blood or represented by a determiner in the germ plasm. Any variability in the hypothetic structural formula for a blood group is untenable. There are four blood groups known today and, as the theory of heredity is based on the belief of a specific determiner for each hereditary character, transmissible through the germ plasm, I believe in the existence of four separate and distinct biological determiners for the blood groups. The whole story of the origin of the blood group is not told in the blood of the parents of a family, and the fact must ever be kept in mind that ovaries and testes are the vehicles through which past and present biological characters of man are linked together. If the function of germinal tissues to segregate and transmit characters to subsequent generations is ignored, worthless hypotheses and formulas will be established in order to explain an evident character occurring in man. A curious situation would exist in the family represented in Fig. 5, if the criteria of Ottenberg were accepted. The twins were in different groups, and one was in a group different from that of either parent. The danger of drawing conclusions from

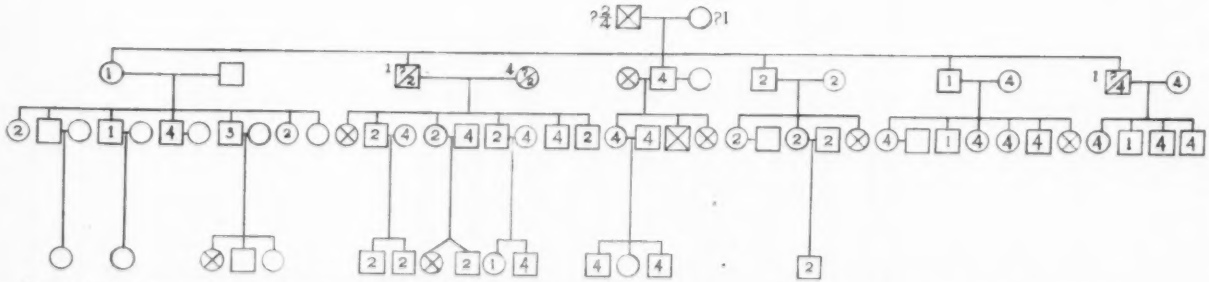


FIG. 13.—The parental generation in this family (Tink) can be presumed to be a heterozygous male (Groups II and IV) crossed by a homozygous female (Group I). The segregation of these characters in the first generation is striking. Additional undetermined groups are introduced into the second generation by marriage. If the heterozygous status of man for the blood group were not demonstrable the appearance of the Group IV in the third generation of the second family, and the Group I in the third generation of the sixth family and in the fourth generation in the third family would be inexplicable by the science of heredity. The difficulties in the medico-legal application of the blood group are sharply shown in this family and the inability to prove by the study of isolated small families the transmission of the blood group by the germ plasm. (Information obtained through the courtesy of Mr. F. T. Jung, Sheboygan, Wisconsin.)

two-generation studies is shown in Figs. 13, 14, 15, 16, and 17. Such families are without conclusive value in the study of the inheritance of the blood group, (Figs. 19 and 20) and dangerous when

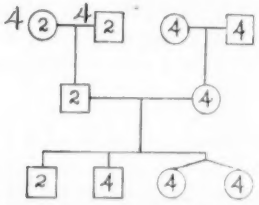


FIG. 14.—Transmission of blood Groups II and IV through three generations and the occurrence of twins of the same blood group.

utilized as criteria to establish the usage of the blood group in medico-legal affairs. There are more than 200 small families or parts of families on record at the Mayo Clinic.

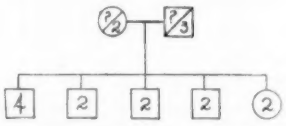


FIG. 15.—Crossing of blood Groups II and III. The result demonstrates the inability to determine parentage from a two generation study of the blood group.

Alexander,[2] in 1921, made an investigation in order to determine if Mendel's second law was fulfilled in the transmission of blood group. He came to the conclusion, in malignancy in particular, "While persons belonging to all four groups are liable to malignant disease, those in Groups I and III appear to be peculiarly susceptible,

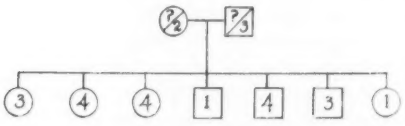


FIG. 16.

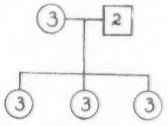


FIG. 17.

FIG. 16.—The frequency of additional groups besides those represented in parents is due to scarcity of pure Group III and the frequency of heterozygous Group II.

FIG. 17.—Demonstrates the necessity for at least four children for the study of the segregation of characters.

and the clinical type of disease is, generally speaking, more malignant." He believed this situation arose by linkage of the factors for cancer and for blood group. The investigations of Higley and myself[8] on material collected by Sanford in the Mayo Clinic showed this conclusion to be incorrect. In a study of 2446 persons with

various diseases we found that there were no evidences of linkage. There was no evidence that a person in a particular blood group

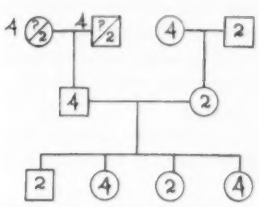


FIG. 18.

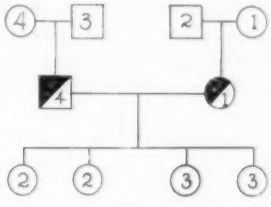


FIG. 19.

FIG. 18.—Transmission of blood Groups II and IV through three generations demonstrating the heterozygous nature of one of the parents on the left in the parental generation.

FIG. 19.—If this family had been grouped through two generations only, it could be believed that the resulting groups were simply the product of a rearrangement of specific substances *A* and *B*, and *a* and *b*. A review of an earlier generation gives the clue to the groups to be expected in subsequent generations. The blood of parents in the second generation was in Groups IV and I, but all four groups were present in the germ plasm. The dormant characters reappeared and, it must be admitted that the evident characters would have appeared had the family been sufficiently large to permit of segregation of all the determiners for blood group in the germ plasm. If not, blood group is not hereditary. An attempt to state that unions of Groups I and II, and Groups I and III can only give rise to similar groups is to ignore the possible heterozygous state of a parent. Unions with Group IV or of Groups II and III give rise to all groups because persons who are pure for the common groups, Groups II and IV, are very difficult to find; it is still more difficult to find persons who are pure for the rare groups, Groups I and III.

was more susceptible to a certain disease and the reactions to disease were practically the same in all blood groups.

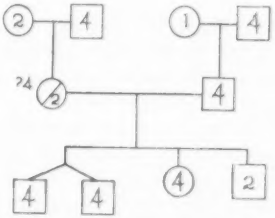


FIG. 20.—In this family three groups were crossed in the first generation. The members of the second generation showed only one group in their blood unless the blood group of the third generation is studied, there is no way of determining the heterozygous or homozygous nature of the parents in the second generation. If the numerical superiority of one character to another is a fixed thing in man, either Group II or Group IV should constantly recur in greater numbers when they are crossed. Other families studied indicate that Group II appears with greater frequency when crossed with Group IV. The female of the second generation may have Groups II and IV in her germ plasm but at present this cannot be proved.

The percentage relationships of the blood groups in the two sexes did not vary in 2176 groupings of 1245 males and 931 females.

The percentage distribution in the males was Group I, 3.69 per cent; Group II, 40.97 per cent; Group III, 9.39 per cent; and Group IV, 45.77 per cent. In the females the distribution was Group I, 3.97 per cent; Group II, 41.46 per cent; Group III, 8.69 per cent; and Group IV, 45.85 per cent. The families represented in Figs. 1 to 21 demonstrate the transmission of the blood group between males and females without regard to sex. There are no evidences of sex linkage in the transmission of the blood group.

The second law of Mendel, namely, the independent assortment of characters, so far as data at present are concerned, is fulfilled by the blood group.

Comment. The blood group is an expression of a hereditary character of man. There are four characters known at present which are arbitrarily designated Group I, Group II, Group III, and Group IV. The blood is transmitted by the germ plasm according to the first and second laws of Mendel. The hybrid stage is absent.

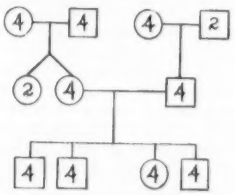


FIG. 21.—Segregation of pure blood Group IV from the parental generation as shown by all the children being in the same group. The twins are in different groups which demonstrates the heterozygous nature of one of the parents, and the peculiar segregative power of the germ plasm.

Whether the Jansky or Moss classification is used in this study of the inheritance of the blood group is not of importance. The groups may be classified by either method and are transmitted between generations in accordance with the same rules. There is no method available at this time by which a strict or presumptive delimitation of the blood group possible in children resulting from the union of two persons can be made. Careful investigation conducted into the ancestry of every generation must be carried out in order to ascertain the blood group possibilities in any family, and even then the medico-legal application of blood groups will be surrounded with many difficulties.

The blood group offers a concrete means for the study of heredity in man.

INHERITANCE OF MIGRAINE: STUDY II. The demonstration of the transmission of migraine through generations by means of the germ plasm transfers the condition from the category of disease to that of biological character of man. The term "migraine" designates an unknown physiological process which is recognized by

periodic attacks of pain, usually in the head, either unilateral or bilateral, but occurring also in the abdomen, and in either location frequently associated with nausea, vomiting, mental depression, visual phenomena, and many vague somatic disturbances. One or all of the symptoms may occur in an attack, which lasts from a few to several hours or days. The first expression of the character appears early in life, and as a rule, the manifestations disappear during the fourth decade.

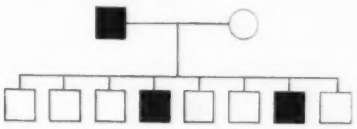


FIG. 22.—The segregation of the migraine character in families in which a person with migraine and a person without migraine have been crossed.

Studies instituted to prove migraine expressive of a hereditary character must of necessity include the investigation of parents and at least four children in families in which there were unions of a person with migraine to a person without migraine, of known heterozygous persons, or of two persons with migraine. "Without migraine" is the contrasted character. Under like conditions, the segregation of the character will occur among the children in a fairly definite manner.

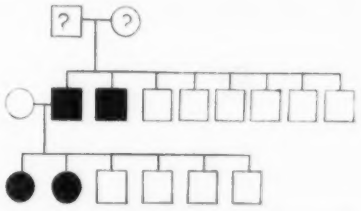


FIG. 23.—The value of searching for all the evidence available in a family in which one member has migraine. It can be presumed that a parent in the first generation had migraine because of the distribution in the second generation. The segregation is carried into the third generation.

The Distribution of Migraine in Families.[9, 10] A study was made of 127 families, one or more representatives of which were examined in the Mayo Clinic in 1919. Migraine followed the two laws of Mendel (Figs. 22, 23 and 24). Of the total number of children in the 127 families, 198 had migraine and 610 had the character, without migraine. At the time the study was reported a combined Mendelian ratio was calculated for all the families studied. This ratio was incorrect, as amalgamation of the crosses was contrary to

the scheme of Mendel. The ratios were correct for the individual groups. The same difficulties exist in working out a Mendelian ratio for migraine as exist for the blood group.

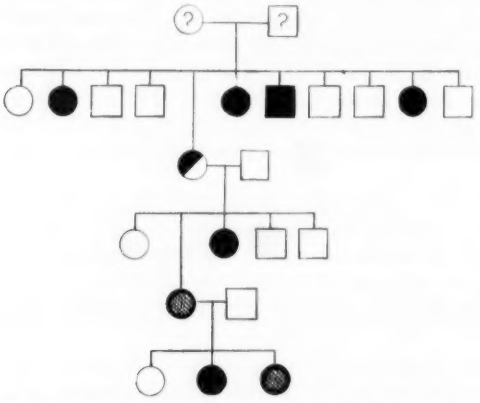


FIG. 24.—Transmission of migraine with abdominal crises.

Like all hereditary characters migraine exists in either the homozygous or the heterozygous state. The heterozygous state (Fig. 25) has led many writers to say that migraine is hereditary in 90 per cent of instances and in various other percentages, because it occurs in a number of families in which it is not demonstrable in the parents. During the last two years many cases in the Mayo Clinic have been

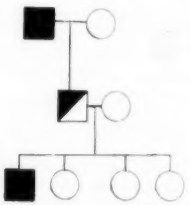


FIG. 25.—The heterozygous status of the male of the second generation as shown in the appearance of the character in the final generation.

observed, in which migraine was not present in the parents, but present in the brothers or sisters, if the family was sufficiently large or present in one or the other of the grandparents. Data derived from patients having no knowledge of their parents and grandparents are not usable as evidence for or against the Mendelian transmission of migraine. Such information is valueless on either side of the question. It is to be remembered that by means of the

heterozygous status of certain persons a character may be transmitted through many generations of small families without any signs of its presence. The character may appear in the first large family.

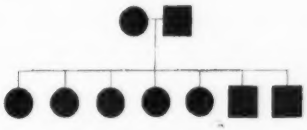


FIG. 26

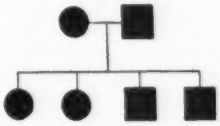


FIG. 27

FIG. 26.—Cross of persons with the pure migraine character.
FIG. 27.—The union of homozygotes results in all offspring having the same character.

The homozygous state of migraine has been studied in three families in which both parents had migraine. If migraine exists in a homozygous states, all children resulting from such unions should have migraine. This occurred in the three families studied (Figs. 26, 27 and 28). Although this is an interesting observation,

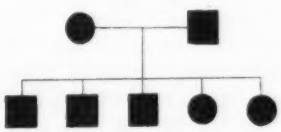


FIG. 28.—If migraine is heterozygous for families without migraine, individuals without the character should be segregated in families of four or more children. The absence of such segregation is illustrated in this family.

the data are too meager to be of value in determining if the relationships of the dormant and evident phases of migraine are reversible. It may be that a person with migraine may become the parent of children without migraine, just as it has been shown that the relationships of the blood group in the heterozygote are reversible. This subject requires careful study.

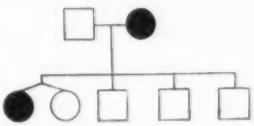


FIG. 29.—The segregative power of the germ plasm. One twin had migraine the other was without migraine.

One family has been studied (Fig. 29) in which there were twins; one had migraine and the other did not have migraine. This is interesting when compared with the appearance of different blood groups in twins (Fig. 5).

In the description of the causal factors for a number of diseases, various writers have given migraine as one of the etiological factors. So far as is known, the determiner in the germ plasm for migraine has nothing to do with the production or evolution of any character other than itself. The migraine determiner is as specific for itself as the determiner for a particular blood group is for itself. Any disease may occur in the person with migraine. It is an association and not an etiological relationship.

Comment. Migraine is the expression of a hereditary character, but the physiological processes which occur at the time of the manifestation of its phenomena are unknown. It is not possible to change the blood group by either surgery or drugs, so it does not seem reasonable to expect that migraine which is a similarly derived character could be influenced by any of the procedures recommended. Patients with migraine who have been examined in the Mayo Clinic demonstrate the futility of all sorts of treatment. Evidence has not been accumulated to substantiate the belief that a "tendency to migraine" is inherited; "migraine" and "without migraine" are the inheritable characters. A person either has or does not have migraine, just as a person always belongs to a blood group.

Inheritance of Essential Epilepsy: Study III. There is no gross pathological basis for the explanation of the seizures of essential epilepsy. It is characterized in man by periodic seizures in which there is loss of consciousness, preceded by more or less marked prodromal sensations, and followed by and associated with tonic or clonic spasms of the general musculature. The seizures last from a few minutes to one hour or more, and their frequency is variable. A seizure in which there are severe convulsions and loss of consciousness is termed "grand mal." A milder form in which vertiginous or momentary blank sensations replace the convulsions is termed "petit mal." Hippocrates believed that essential epilepsy began in utero, and as a consequence of this belief and the absence of a pathological basis, many diseases such as neurasthenia, hysteria, insanity, and the undefined group of diseases known as nervous disorders or neuropathies have been incriminated as causal agents. St. Hildegard seems to have been one of the earliest writers to suspect that migraine and essential epilepsy were expressive of the same entity.

The Relationship of Migraine to Essential Epilepsy. In order to obtain data on the relation of the various neuropathic influences to essential epilepsy, two series of cases observed in the Mayo Clinic were analyzed. The results warranted the dismissal of all of the so-called nervous disorders as related factors, since they occurred not more often in the ancestral history of persons with essential epilepsy than in the ancestral history of persons with diseases of known etiology. Migraine is the only character which appeared with enough frequency to attract attention. In the first

series of 128 cases,[7] migraine occurred in the ancestral or personal history or in that of the brothers and sisters in 53.9 per cent of the cases. The 128 cases comprising the second series had been carefully studied in the Section on Neurology of the Clinic and of these cases 66.4 per cent gave a history of migraine in ancestors, brothers or sisters or in the personal history. In the former series migraine was present before the onset of essential epilepsy and alternated with or continued with epilepsy in 14 per cent of the cases studied. In the latter series, this occurred in 10.5 per cent of the cases. The genetic relationship of migraine to essential epilepsy seemed to be quite striking.

The Familial Distribution of the Migraine-epilepsy Character. If essential epilepsy is expressive of the same underlying biological factor on which migraine depends, its appearance in families would not disturb the relationship of persons with migraine to persons without migraine; it would simply replace or alternate with the migraine character in certain persons. The same laws and requirements that govern the transmission of the blood group or migraine alone would be followed and fulfilled.

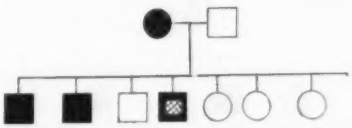


FIG. 30.—The failure of essential epilepsy to disturb the numerical relationship of normal persons to those with the inherited character. Essential epilepsy is superimposed on an individual with the migraine character.

Essential epilepsy on empirical grounds was considered as simply another phase of the phenomena of the migraine character in a study of 47 families whose histories were complete for ancestral data. The contrasted character was "without migraine-epilepsy," or what is commonly called the normal. The same segregation of characters was seen as when considering migraine alone (Figs. 30, 31 and 32). At a subsequent date, 35 similar families were studied, and the data obtained in the first families were altered in no way. In a certain number of the patients studied, varying in all series from 10 to 14 per cent, migraine and epilepsy alternated irregularly.

If essential epilepsy is expressive of the same phenomena as migraine, the marriage of an epileptic person to a migrainous person would result in all of their children having migraine or all or part having essential epilepsy. One family has been found to fulfil this condition; all the children had migraine, and in 1 the migraine alternated irregularly with epileptic attacks (Fig. 33).

If essential epilepsy depends on the factor of migraine for its

evolution, the marriage of homozygotes or heterozygotes for migraine should result in the production of a certain number of children

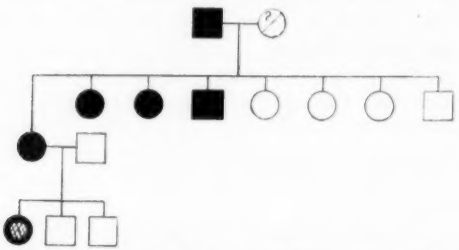


FIG. 31.—The number of persons in the second generation with migraine is greater than is to be expected from a cross of a pure migraine with a pure normal. This has been observed in several families and is considered due to the heterozygous, although unproved, status of the apparently normal parent. The character appears as essential epilepsy in the final generation.

subject to seizures of essential epilepsy. The marriage of two persons with migraine is quite rare and as a consequence the opportunity

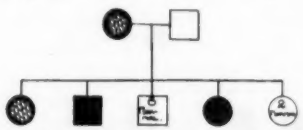


FIG. 32.—The mother had epilepsy in early life, replaced by migraine. The same segregation of the characters occurred as if the mother had always presented migraine.

to observe the frequency with which a child with essential epilepsy should result from such unions would be very infrequent. I have

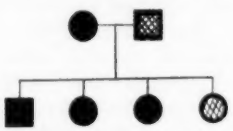


FIG. 33.—The crossing of a migrainous person with an essential epileptic person. The character, epilepsy, behaves as does the character, migraine.

found the record of only 1 family (Fig. 34) which furnished any information on the subject in the files of the Mayo Clinic. Many

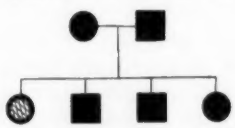


FIG. 34.—The results of crossing two persons with migraine.

families (Figs. 35 and 36) have been found which demonstrate the heterozygous property of the normal to transmit migraine, essential

epilepsy, or both to their children, because of the strain which had been introduced into their germ plasm by the grandparents.

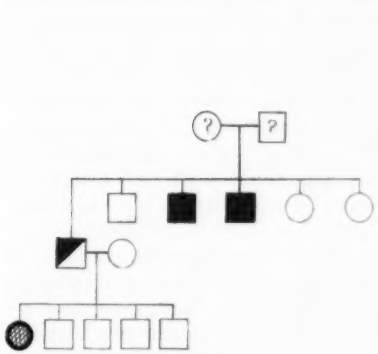


FIG. 35

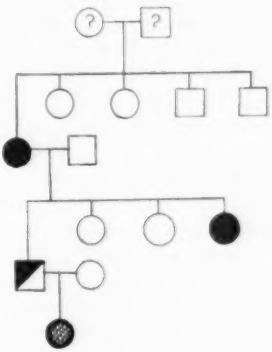


FIG. 36

FIG. 35.—The transmission of the migraine-epilepsy character because of the heterozygous status of the male parent.

FIG. 36.—The heterozygous status of the germ plasm and its segregative power. The final generation studied would have no value if considered by itself without information obtained from other families.

Comment. Essential epilepsy and migraine are transmitted from generation to generation as the expression of the same underlying factor in the germ plasm. The mechanism for the production of the seizures is unknown. The organic factors capable of producing phenomena similar to those of essential epilepsy are so numerous that the classification of an individual in the class with essential epilepsy demands extreme caution.

A diminution in the number of essential epileptics by segregation in colonies is not to be hoped for, as the person with migraine is more likely to produce epileptic offspring than the epileptic person himself.

The theory that essential epilepsy and migraine are the expression of a biological character, and their manifestations are, therefore, physiological needs offer no insurmountable obstacles in its acceptation. If it is possible for such striking characters as waltzing in a mouse and tumbling in a pigeon to be hereditary there is no reason why characters equally striking might not appear in man. The management of migraine and essential epilepsy as expressions of biological characters undoubtedly will result in a greater degree of happiness and health than has hitherto been possible for those individuals because of the unlimited and ever-varying type of operation and drug therapy which has been carried out without benefit.

DIABETES MELLITUS: STUDY IV. From the earliest history of diabetes mellitus references have been made to heredity as an

explanation for the occurrence of a varying percentage of cases of the disease. The reported families were compiled, in 1912, by Foster[19] who at the same time reported a family observed by himself. In practically all of the articles on the subject, mention is made of the number of persons in the family who were afflicted, but no mention is made of those who were in good health. The 3 families reported by Long[26] are noteworthy exceptions. Von Noorden,[33] Naunyn,[32] May[28] and more recently, Allen[3] have called attention to the importance of heredity in diabetes. Allen suggests that the subject should be studied by the methods used by biologists in determining hereditary characters, as no attempt has been made to study the condition in the light of the laws of heredity.

If diabetes mellitus is to be considered as representative of a unit character, it would be interpreted as a physiological expression of a cycle in the life of certain persons, whereby they would lose the power to metabolize carbohydrates and as a consequence a portion or all of the sugar ingested, the stored carbohydrates, and a portion of the body protein and ingested protein are converted into sugar and excreted as such in the urine. At the same time the chemical changes which result in coma and death would be the final expression of this lethal cycle. The contrasted character would be what is called "normal," or that possessed by a person whose carbohydrate metabolism is constituted so that the phenomena of diabetes mellitus do not appear. The families should be studied through two generations, and at least three and preferably four children should be present in the families used for study.

Diabetes Mellitus not a Mendelian Character. Diabetes mellitus, if hereditary, must conform to the known laws of heredity. To determine if such be the case, the progeny of persons with diabetes mellitus married to persons without diabetes mellitus have been studied. The material consisted of 34 families, 17 of which were studied through two generations and 17 throught three generations. The total number of diabetic offspring was 65; 274 were without any evidence of diabetes mellitus at the time the data were collected. Sixty-five children (16.08 per cent) died in early life.

The results of unions (Figs. 37, 38 and 39) of diabetics (homozygotes) and non-diabetics in the cases studied revealed no information to show that the condition was transmitted through the germ plasm. The occurrence in the children did not conform to the Mendelian laws. Further investigation in these same families may reveal information of great value.

Occasional families have been observed (Fig. 38) which suggested the possibility that diabetes mellitus might be transmitted to a subsequent generation because of the heterozygous state of a parent. A study to throw definite light on this subject was made in 18 families, of which 11 were studied through two generations, and 7 through three generations. There were 18 children with

diabetes, and 126 without. Thirty-five of the children (19.05 per cent) died in early life. The impression that diabetes might be transmitted through the germ plasm on account of the heterozygous

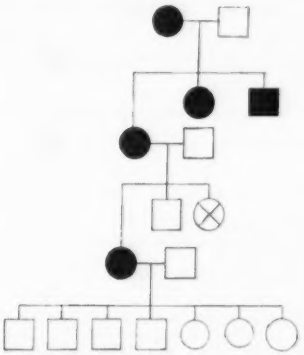


FIG. 37.—A family in which diabetes mellitus has occurred for three generations. It appeared in the mother of the last generation at the thirty-third year. None of the children were affected at the time the patient was investigated.

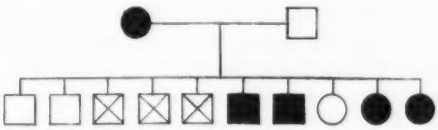


FIG. 38.—The results of crossing the diabetic and non-diabetic persons. The number of diabetic offspring is too large, as the father's family was free from diabetes. Three children died in early life, presumably free from diabetes mellitus.

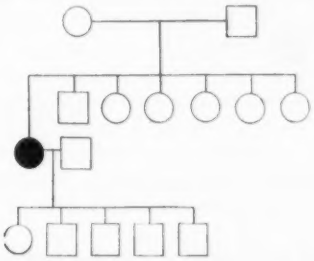


FIG. 39.—The failure to conform to known laws of heredity is shown in this family Diabetes if hereditary would have appeared at the age of sixty-two or thereabouts in at least two children in the second generation.

nature of a parent was not supported by the data obtained from the 18 families studied. These families are typified in Fig. 41.

If diabetes mellitus were hereditary, homozygous and heterozy-

gous individuals would result from the crossing of a diabetic person with a non-diabetic. The failure of the homozygous principle to be supported has been shown in the cases of diabetes reported by Crofton and others in which it has been found that both parents may have diabetes mellitus and none of the children be afflicted.

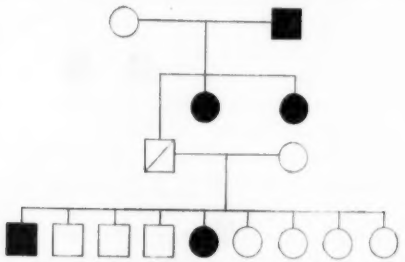


FIG. 40.—This group suggests that diabetes mellitus might be transmitted through the germ plasm because of the heterozygous nature of the male parent of the second generation.

The lack of conformity to the laws of dominance and recessiveness in man because of the absence of the hybrid stage may explain certain discrepancies in the familial occurrence of diabetes, but neither the homozygous nor the heterozygous principles in heredity have been fulfilled by diabetes mellitus.

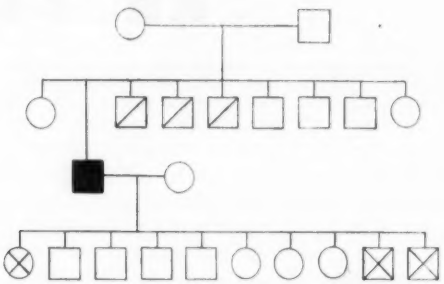


FIG. 41.—A family illustrating the families studied to determine if diabetes mellitus is transmitted by a heterozygote.

Method for Collection of Data. The methods used today for the collection of data in families where diabetes mellitus occurs are not such as will ever result in obtaining data of conclusive value. To prove diabetes mellitus hereditary, a cyclic nature of the disease would have to be postulated, that is, the condition would make its appearance at approximately the same age and have a definite progress in a certain number of the members of the family. There-

fore, data should be obtained in each family concerning: (1) The time of onset in the parents; (2) the number of brothers and sisters of the parents and the age of each; (3) the age of each at onset of diabetes; (4) the number of children in the last generation; (5) the age of each child when the condition appeared; and (6) the ages of those at or beyond the age at which it appeared in the parents. The collection of the data would necessitate a follow-up system of investigation and a study of the children as they arrived at the proper age. In no other way will it be possible to prove that conditions like diabetes mellitus should be transferred from the status of a disease to the list of conditions in man which are expressive of a biological character transmissible through the germ plasm. The data presented in my study did not fulfil these requirements. So far as the data collected are reliable, there is not the slightest evidence to justify the statement that diabetes mellitus is at times hereditary. There is also insufficient evidence to show that the condition is not hereditary, but the evidence does point more toward the quantitative action of some causal factor rather than the expression of the segregative properties of the germ plasm.

The high mortality in early life of children born of diabetic parents is striking.

Essential Asthma: Study V. In essential asthma, as in all conditions in man the etiology of which is obscure, the mechanism of heredity has been believed to play an etiological role. Geddings[20] reviewed the statistics of the earlier writers, and came to the conclusion that the tendency to essential asthma is hereditary. All of the earlier writers, with the exception of Drinkwater,[17] reported a percentage of inheritance of essential asthma varying from 10 to 50 per cent. Drinkwater reported his families as expressive of the segregative power of the germ plasm. The more recent literature has been reviewed by Adkinson,[1] who at the same time presented data obtained from a large number of cases. She found a family history of essential asthma in 48 per cent of the 400 cases studied, and came to the conclusion that asthma is hereditary in a varying percentage of cases. She also concluded that asthma appeared at an earlier date in the children than in the parents. If asthma is a hereditary character it must have been present in man since his appearance on earth, as there is no way for hereditary characters to be kept extant except by breeding of those in whom the character is present. The known period of man on earth has been computed to be millions of years. Essential asthma was distinguished as a distinct clinical entity by Willis[47] about 1600. If a character were present in primeval man, or even since 1600, and appeared at a perceptibly earlier age in the children of each generation, the cycle required for its appearance would eventually be brought down to a period earlier than the performation of the embryo, or in the germ plasm, and

after it had arrived at that state would of necessity either have to disappear, or by some miraculous process again revert to appearance in old age. This claim is made for other conditions in man, but there is no evidence in heredity to support such a hypothesis.

An investigation to demonstrate the transmission of essential asthma to subsequent generations by the germ plasm must be conducted in the same manner as that for migraine. It would be transmitted in exactly the same manner, and follow the same rules of heredity. For this reason a small number of families would be sufficient to establish the hereditary character of the condition. The contrasted character would be "without asthma."

The families presented in Tables I and II are sufficient to justify a conclusion in regard to the hereditary nature of essential asthma. In families used for the study the children had reached the age at which the condition appeared in the parent. In the 17 families in Table I there was evidence of asthma in parent and offspring. This does not warrant the conclusion that asthma is hereditary. The law for the segregation of characters is not followed to a degree in any way approximating the numerical ratio for hereditary characters. In Table II the data presented does not lead to the conclusion that asthma was transmitted in these families as a result of a heterozygous state of one or the other parent. If a character or condition under consideration does not follow the course of either the homozygous or heterozygous type for hereditary characters, it is safe to conclude that the condition is not hereditary. The study of a larger group of similar families would show the same figures.

TABLE I.—TRANSMISSION IN SEVENTEEN FAMILIES IN WHICH FATHER OR MOTHER HAD ASTHMA.

	CHILDREN.	
Asthma in.	With asthma.	Without asthma.
Mother	1	14
Father	..	5
Mother	2	7
Mother	1	4
Mother	1	3
Mother	1	8
Mother	..	6
Father	..	4
Father	..	4
Mother	..	3
Father	..	5
Mother	..	8
Mother	..	9
Father	..	5
Mother	2	6
Father	..	7
Father	..	4
	8	102

TABLE II.—TRANSMISSION IN THIRTY-NINE FAMILIES IN WHICH NEITHER FATHER NOR MOTHER HAD ASTHMA.

CHILDREN.					
With asthma.	Without asthma.	With asthma.	Without asthma.	With asthma.	Without asthma.
1	7	1	5	1	12
1	7	1	7	2	3
1	3	1	6	1	4
1	3	1	5	1	5
1	7	1	9	2	3
1	4	1	4	1	5
2	3	1	6	1	5
1	3	3	4	1	6
1	3	2	12	1	5
1	12	1	6	1	5
1	6	1	7	1	7
1	3	1	8		
1	9	2	4	—	—
1	9	1	4	46	226

Comment. Essential asthma in its familial appearance follows none of the known laws of heredity. It is not the expression of a specific hereditary biological character of man.

PROTEIN SENSITIVITY: STUDY VI. Protein sensitivity has been attributed by Osler,[36] Oppenheimer and Gottlieb,[35] Walker,[45] Longcope,[27] Barber,[6] Cooke[13] and others to the inheritance of a particular type of sensitive cells which react in a particular way when subjected to the influence of various protein substances. This belief permits of a very important investigation in man.

For many years "the inheritance of suceptibility to certain states" has been believed. If such be the case, the suceptibility must be transmitted in accordance with the laws which govern the inheritance of all characters. The mating of a person with protein sensitivity to a person without protein sensitivity, if the condition were dependent on the transmission by the germ plasm of a particular type of cellular protoplasm, would result in the production of a certain number of children of this susceptible type, some of whom would be heterozygous, others homozygous. If the children of such crosses were exposed to the same conditions of protein influence, and they would be so long as they lived under the same climatic and seasonal environments, those who inherited the peculiar type of somatic cells would react to the foreign substance in such numbers as to fulfil the Mendelian law for the segregation of characters. The possibility of the inheritance of a type of cellular structure that is susceptible to certain influences could be demonstrated under no more propitious circumstances.

The Familial Occurrence of Protein Sensitivity. In order to investigate the possibility of inheritance of the susceptibility to foreign protein, I have studied a small number of families in which there was parental protein sensitivity, and a larger group in which there was no parental sensitivity to proteins.

The number of families studied in Table III is very small, but the segregative property of the germ plasm does not wait until the hundredth family. The segregation will appear in the first family studied as well as in the last. There is no evidence in these families that the germ plasm carried any factor on which the protein sensitivity depended.

The 24 families of Table IV consisted of 28 children with protein sensitivity and 126 without. The families might be considered as expressive of the transmission of the condition by a heterozygous parent. This assumption is disproved by the failure of protein sensitivity to reappear in the third generation of certain families of Tabes III and IV. Hereditary characters are carried on forever, otherwise, the theory of germinal continuity would be false, and there is no obvious reason why an exception should be made in the case of protein sensitivity.

Comment. A consideration of the families represented in Tables III and IV leads me to the conclusion that protein sensitivity is not dependent on the transmission through the germ plasm of a factor which is responsible for the appearance of the condition in man. Furthermore, the data presented are criteria against the continuation of the use of the expression, "inheritance of susceptibility to disease." No evidence has been presented in the study of heredity to show that characters are susceptible of appearing or that there is a tendency for them to appear. They are either present or absent. There is no uncertainty.

TABLE III.—THE FREQUENCY OF PROTEIN SENSITIVITY IN CHILDREN OF SEVEN FAMILIES WHEN PRESENT IN ONE PARENT

	CHILDREN.	
Protein sensitivity in.	With protein sensitivity.	Without protein sensitivity.
Mother	1	3
Mother	..	6
Mother	1	11
Mother	..	4
Mother	..	4
Father	..	4
Mother	..	4
	2	36

TABLE IV.—THE FREQUENCY OF PROTEIN SENSITIVITY IN CHILDREN OF TWENTY-FOUR FAMILIES WHEN ABSENT IN PARENTS.

CHILDREN.					
With protein sensitivity.	Without protein sensitivity.	With protein sensitivity.	Without protein sensitivity.	With protein sensitivity.	Without protein sensitivity.
1	5	1	6	1	7
1	4	1	6	1	5
1	9	1	3	1	5
2	2	2	5	1	4
1	4	2	2	1	3
1	3	1	3	1	6
1	5	1	6	1	5
1	9	1	7	1	6
				28	126

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TOLYSIN IN ACUTE RHEUMATIC FEVER AND OTHER CONDITIONS.

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Ethyl ester of paramethylphenylcinchoninic acid (tolysin) has received recent recognition as an improvement over salicylates in acute rheumatic fever and other conditions. In particular, Hanzlik, Scott, Weidenthal and Fetterman[1] employed it in 3 cases of acute rheumatic fever and observed complete relief after 11 to 16 gm. had been given. These authors point out that the drug appears to be quite innocuous in large doses and is less irritating than cinchophen or the salicylates that are usually given. Accord-

ing to their evidence and that of Chace, Myers, and Killian[2] the function of the kidneys appears to be stimulated in some cases by tolysin.

Two of the present authors[3] have recently demonstrated that tolysin exhibits an unusual lack of toxicity. It is impossible to injure dogs in any way with doses amounting to 5 per cent of their body weight; it is nevertheless an efficient antipyretic in these animals in small doses. It was found that this is due to an unusual coincidence between the maximum therapeutic dose of tolysin and the maximum amount which can be absorbed from the intestine.

Such a drug seems to offer possibilities as a partial, if not a complete, substitute for the salicylates which are now in use, all of which require constant attention to the avoidance of toxic symptoms. In the following report, therefore, we shall present evidence as to the clinical value of tolysin.

The cases herein described are from the wards of the Montreal General Hospital, service of Dr. F. G. Finley, and the Royal Victoria Hospital, service of Dr. C. F. Martin, and include also a number of private observations.* They will be presented under the headings:

1. Acute and subacute rheumatic fever.
2. Other cases of arthritis.
3. Observations on tolysin as an antipyretic and analgesic.

1. Acute and Subacute Rheumatic Fever. 12 individuals suffering from rheumatic fever were treated with full doses of tolysin; one of these received two courses of the drug, having suffered a relapse in the interval, for which he was unsuccessfully treated with salicylates. The routine dosage finally determined upon was 2 gm. every two hours for three doses, followed by 1 gm. every four hours (four or five times a day). In a few of the earlier cases were made some unimportant differences in the dosage and interval. The details of this series are presented in Table I.

It will be noted from the above that, with two exceptions, the amount necessary for complete relief (by which is meant cessation of fever, pain and swelling) varied from 10 to 16 gm. To this may be added the fact that partial relief was usually noted after 7 to 8 gm. had been given.

In several cases the drug was continued over a longer period of time than absolutely necessary in order to demonstrate its non-toxicity. 2 different patients received 50 gm. of tolysin within eight days. Similarly, a patient not included in the present series received 24 gm. within forty-eight hours. As reported in our laboratory paper, this 24 gm. of tolysin was completely absorbed, none being recoverable from the feces. In none of these 3

* The authors desire to express their appreciation of the coöperation of Professors Finley and Martin and their respective staffs, including especially Miss Jackson of the Montreal General Hospital.

Case No.	Name.	Age.	Sex.	Clinical diagnosis	Tolysin giving complete relief.	Total number of grams administered in number of days.		Gastric symptoms.	Albuminuria.	
					Gm.	Gm.	Days.		Before treatment.	After treatment.
1	A. C.	40	M.	Acute rheumatic fever	16	26	7	None	0	0
2	J. F.	14	M.	Relapse, acute rheumatic fever	6.5□	6.5□	3	None	0	0
3	S. M.	49	M.	Acute rheumatic fever	16	38	5	None	0	0
4	N. D.	28	M.	Acute rheumatic fever	12	54	7	None	++	Trace
5	H. B.	35	M.	Acute rheumatic fever	14	50	8	None	Faint trace	0
6	E. B.	24	M.	Subacute rheumatic fever	10	13	4	None	0	0
7	A. S.	17	F.	Acute rheumatic fever	10	21	7	None	0	0
8	R. S.	23	M.	Acute rheumatic fever	16	24	6	None	Faint trace	0
9	J. M.	24	M.	Acute rheumatic fever	40[1]	40	10	None	Faint trace	0
10	H. C.	38	M.	Acute rheumatic fever	16	24	6	None	0	Faint trace
11	L. F.	18	F.	Acute rheumatic fever	14[2]	18	6	None	Faint trace	0
12	W. W.	37	M.	Acute rheumatic fever	16[3]	60	14	None	Faint trace	0
"	"	"	"	Relapse[5]	16[4]	24	8	None	0	0

[1] Sodium salicylate, 3 grams per diem for six weeks, had given partial relief.
[2] Sodium salicylate, 4 grams per diem for eight days, had given partial relief.
[3] Every symptom relieved except one slightly painful shoulder.
[4] Preceded by eleven-day interval of sodium salicylate treatment (48 grams in all).
[5] Occurred during salicylate treatment.

instances of high dosage were noted any untoward symptoms whatever.

In fact, in all cases in which we have followed the results of tolysin treatment, nausea, vomiting, excessive sweating and cardiac depression have been absent. So-called "salicylism" is not induced even by relatively large doses. Complaints of gastric disturbance were not elicited, although carefully sought.

Albuminuria, which was present in 6 of the 12 patients on admission, disappeared in 5 of these during treatment; in the sixth the albumin became diminished to a trace. Improvement in this respect may presumably be attributed to rest in bed and restricted diet. In only 1 of the 12 cases did albumin first appear or increase in amount during treatment with tolysin.

Below are given the chief points in the clinical histories of patients with acute rheumatic fever. Temperature Charts I to III are also illustrative.

CASE REPORTS. CASE I.—A. C., male, aged forty years. March 3, 1922. Admitted to hospital complaining of pain and swelling in joints.

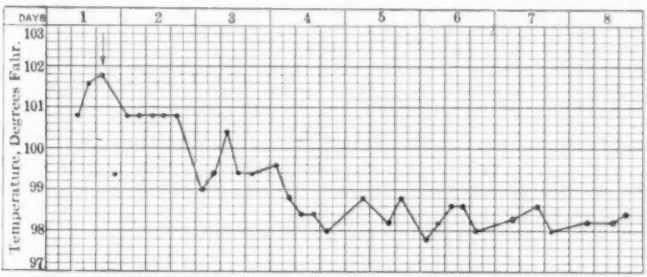

FIG. 1.—Case 1. Acute rheumatic fever. Readings every four hours. Tolysin 1 gm. every two hours for 3 doses, then 1 gm. every four hours started at arrow. Relief from symptoms coincident with fall in temperature.

Present Illness. On February 11, 1922, patient got his feet wet and three days later pain and swelling of right ankle and foot caused him to take to bed where he remained for three days when he apparently recovered and returned to work. Two days later left knee painful for three days but not severe, morning of fourth day left knee very painful, tender and swollen and patient was again forced to his bed. March 22, 1922 pain and swelling of left shoulder, elbow and wrist. March 3, 1922, admitted to hospital.

Treatment. Patient had no treatment at home except iodine painted over painful joints. March 3, Tolysin 1 gm. every two hours for 3 doses then every four hours. March 4, slight fall in

temperature with some relief from pain. March 6, patient free from all pain. March 11, patient discharged, cured. He received in six days a total of 26 gm. of tolysin. Temperature Chart I, is the temperature record of this patient.

CASE II.—J. F. male, aged fourteen years, was admitted to hospital February 17, 1922 with diagnosis of acute rheumatic fever. Treated with salicylates for three days with good results. March 1, patient suffered a relapse, pain and swelling returning in several joints. For this relapse he was given tolysin 0.7 gm. every four hours for 10 doses which gave him complete relief.

CASE III.—S. M., male, aged forty-nine years, was admitted to hospital March 12, 1922, complaining of pain and swelling in joints.

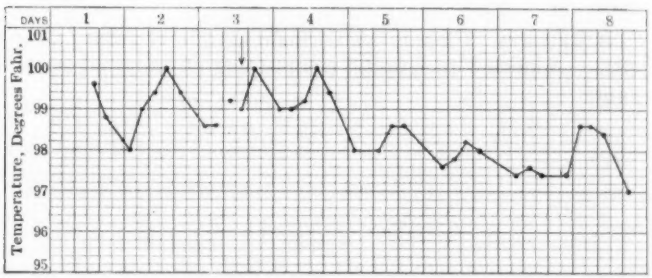

FIG. 2.—Case 3. Acute rheumatic fever. Readings every four hours. Tolysin 2 gm. every two hours for 3 doses, then 2 gm. every four hours started at arrow. Relief from symptoms coincident with fall in temperature.

Present Illness. Patient gives history of recurring attacks of acute rheumatic fever. Present attack started nine weeks ago. Pain first felt in right foot which became swollen, red and tender and remained so for four or five weeks. The joints next involved were the right knee, right hip, left wrist, left knee and right wrist.

Treatment. For first two days in hospital patient was on a sugar tolerance test and he received no medication. On third day 2 gm. of tolysin every two hours, 3 doses, then every four hours; complete relief with subsidence of temperature after receiving 16 gm.; total administered, 38 gm. in five days—no signs of toxicity. Discharged March 30, 1922. Temperature Chart II, temperature record of the patient.

CASE IV.—N. P., male aged twenty-eight years, was admitted to the hospital, March 15, 1922.

Present Illness. Patient's history difficult to get. Diagnosis of acute rheumatic fever made.

Treatment. Tolysin 2 gm. every two hours for 3 doses, then every four hours. Complete relief from 12 gm.; the drug was pushed for seven day during which time he received 54 gm. No toxic effects. Discharged March 31, 1922.

CASE V.—H. B., male, aged thirty-five years, was admitted, March 19, 1922, complaining of pain and swelling of joints.

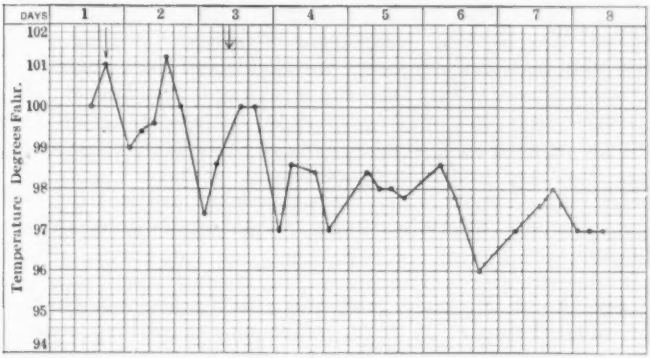

FIG. 3.—Case 5. Acute rheumatic fever. Readings every four hours. Tolysin 2 gm. every two hours for 3 doses, started at first arrow, then 1 gm. every four hours started at second arrow. Relief from symptoms coincident with fall in temperature.

Present Illness. Two weeks ago left foot became painful and swollen, that night he had chills and some fever. Next morning pain less severe in foot but left knee very painful and swollen. In course of next four or five days left shoulder, left wrist and hand involved. Several days later left elbow and right knee involved.

Treatment. Tolysin 2 gm. every two hours for 3 doses, then 2 gm. every four hours. Patient relieved of all symptoms after 14 gm. Drug pushed until 50 gm. had been given; no toxic effects were manifest. Patient discharged March 29, 1922. Temperature Chart III, temperature record of this patient.

CASE VI.—E. B., male, aged twenty-four years, was admitted March 16, 1922, complaining of pain and swelling in joints.

Present Illness. Three weeks ago pain in left big toe, next left ankle then right hip painful. Some fever at onset, pain has persisted until present.

Treatment. Tolysin 0.7 gm. every three hours for 4 doses, then every four hours for four days. Complete relief in four days.

CASE VII.—A. S., female, aged seventeen years, was admitted to hospital, May 10, 1922, complaining of stiffness and pain in joints.

Present Illness. Illness began about six weeks ago with pain in both shoulders and both elbows. Pain more severe at night than during day. Four weeks ago knee-joints involved, followed by left foot and ankle. Since onset of pain, shortness of breath on exertion.

Treatment. Tolysin 1 gm. three times a day, complete relief after 10 gm.; total administered 21 gm.

CASE VIII.—Male, aged twenty-three years, was admitted to hospital, May 20, 1922, complaining of pain and swelling of left wrist-joint, both shoulder-joints, knee-joints and ankle-joints.

Present Illness. Well until two weeks ago. On May 6, 1922, developed pain and swelling in right ankle-joint. Since then pain and swelling with slight redness in joints enumerated above. Some fever and profuse perspiration.

Treatment. Tolysin, 1 gm. every four hours, partial relief after 8 gm.; complete relief after 16 gm. Total administered twenty-four gm.

CASE IX.—J. M., male, aged twenty-four years, was admitted to hospital, February 25, 1922, complaining of swelling, redness, pain and tenderness in ankles, shoulders, wrist and hip-joints. Onset was acute with progressive involvement of the various joints.

Treatment. Sodium salicylate, 1 gm. three times a day was given continuously over a period of six weeks with considerable relief from symptoms. A relapse occurred and sodium salicylate produced some relief from symptoms, but never complete. May 13, 1922, tolysin 1 gm. every four hours, marked improvement after 6 gm. had been given. Administration continued for ten days, with total relief from pain, but some stiffness still present.

CASE X.—H. C., male, aged thirty-eight years, was admitted to hospital, May 18, 1922, complaining of pain in ankle and knee-joints.

Treatment. Tolysin 1 gm. every two hours for 3 doses, then 1 gm. every four hours. Partial relief after 8 gm.; complete relief from pain after 16 gm. although some stiffness still present. Total tolysin administered 24 gm. with continued improvement.

CASE XI.—L. F., female, aged eighteen years, was admitted to hospital, May 9, 1922, complaining of: (1) Pain in soles of feet, ankles, left thumb, left shoulder and small of back; (2) shortness of breath on exertion.

Present Illness. About three weeks ago developed dull aching pain in toes, heels and ankle-joints. The pain was not severe enough to confine patient to bed but was persistent. Later, shoulder and wrist-joints involved, also small of back.

Treatment. On admission, sodium salicylate 1 gm. every four hours for eight days with some relief. May 18, 1922, tolysin 1 gm. three times a day. Patient entirely free from pain after 14 gm.; total administered 18 gm.

CASE XII.—W. W., aged thirty-seven years, was admitted to hospital, April 12, 1922, complaining of pain, swelling and tenderness in joints.

Present Illness. Illness began two weeks ago with a chill, following day pain and swelling of right elbow, and stiffness of finger joints. Two days later both feet and ankles were swollen and painful, then knees and left wrist. On admission, right shoulder shows moderate swelling, tender and very painful on movement. Left wrist, left ankle and right knee also tender but not swollen.

Treatment. April 12, 1922. Tolysin 2 gm. every two hours for 3 doses, then 1 gm. every four hours. Partial relief after 10 gm., patient relieved from all pain after 16 gm. except shoulder, which persisted slightly painful. Tolysin discontinued April 26, 1922, and sodium salicylate 1 gm. three times a day commenced. May 6, 1922, relapse, temperature 101° F., pain and swelling of joints. May 8, 1922, tolysin 1 gm. every four hours, relief after 8 gm.; free from pain after 16 gm. May 15, discharged, free from pain.

2. OTHER CASES OF ARTHRITIS. In 7 further cases of arthritis tolysin was given. The series includes a somewhat ill-assorted list of conditions, especially cases of infective arthritis and chronic joint pains. As will be seen from the following case reports, tolysin gave satisfactory results in all of these except Case XIX, in which severe chronic pains in back and legs were not relieved.

CASE XIII.—L. O'B., female, aged thirty-two years, was admitted to hospital January 19, 1922, complaining of pain in joints and feverishness.

Clinical Diagnosis. Multiple arthritis, infection (tonsil).

Present Illness. On January 15, 1922, headache, sore throat, pain in back, following day severe and steady pain in right shoulder and both elbows with tenderness and slight swelling. January 17, 1922, elbows improved, right knee painful. January 18, 1922, left knee involved also right hand painful and swollen.

Physical Examination. On day of admission, January 19, 1922, Temperature 103.3° F., pulse 128. Both knees and both elbows painful and tender, no redness or swelling; right hand is painful and stiff, right shoulder painful.

Treatment. Sodium salicylate 2 gm. every four hours for 6 doses, then 1 gm. three times daily. During the first few days patient was greatly relieved but pain soon returned varying in severity from day to day, there was a slight degree of pyrexia.

This continued for three weeks. Tolysin February 13, 1922, 2 gm. every six hours was started. At time of administration temperature 100° F., the following day temperature down to 98° and joints less painful. The patient was kept comfortable as long as tolysin was given but pain returned after drug was stopped for two or three days. Relief was again obtained when tolysin was given. Patient discharged March 5, 1922.

CASE XIV.—M. S., female, aged twenty-eight years, was admitted to hospital March 7, 1922, complaining of pain in joints.

Present Illness. Well until five weeks ago, first symptom was pain in the right ankle which became swollen and painful during the past five weeks, one joint after the other became involved, including both sternoclavicular articulations. She was treated with salicylate from the start without improvement. Admitted to hospital March, 7, 1922, temperature 99.4° F., pulse 104, respiration 22.

Treatment. Tolysin, 1 gm. every four hours. Temperature did not become normal until after one week's treatment; pain in joints slowly but certainly relieved, patient ready for discharge April 4, 1922.

CASE XV.—M. J., a female with chronic multiple arthritis of long standing. Patient has taken aspirin for relief of pain but without much alleviation, lately she has been taking tolysin 0.7 gm. four times a day and she feels a great deal of improvement.

CASE XVI.—A female aged sixty-eight years, reported by courtesy of Dr. D. S. Lewis.

Clinical Diagnosis. Diabetes and rheumatoid arthritis, neuritis. Has had severe lancinating pain in right leg for six weeks.

Treatment. Phenacetin 5 gr. three times a day without result; aspirin 5 gr. four times a day, without result; a combination of aspirin, phenacetin and codein with very slight relief. Tolysin, 1 gm. every four hours, began to sleep well again. Pain controlled by 1 gm. twice a day after first forty-eight hours. After two weeks 1 gm. three times a day. After ten weeks 1 gm. four times a day, gave fair control of pain.

CASE XVII.—E. E., female aged forty-seven years, was admitted to hospital, March 31, 1922, complaining of pain and swelling of joints.

Present Illness. Illness began one month ago with a chill following which pain and swelling in left ankle-joint and left knee-joint developed. Patient felt very ill and had some fever, soon right knee, left wrist and right shoulder-joint became swollen and painful. Temperature on admission 99.4° F.

Treatment. Tolysin 2 gm. every two hours for 3 doses, then 1 gm. every four hours. Temperature started to fall after 10 gm. Normal in seven days. Acute pain and swelling rapidly subsided, but patient still complained of stiffness and some pain. Treatment continued over a period of four weeks, with only intermittent relief from symptoms. Urine albumin free and no gastric disturbances.

CASE XVIII.—A. O., male, aged forty-five years, was admitted to hospital, May 8, 1922, complaining of pain in knees, feet, back, elbow and hands.

Present Illness. Well until May 1, 1922, when he developed pain and swelling in left wrist. Four days later pain and swelling in left knee, and both ankle-joints, also pain in back.

Treatment. Tolysin 2 gm. every two hours for 2 doses, then 1 gm. every four hours. Temperature normal after 7 gm. Complete relief from pain after 24 gm. Total drug administered 56 gm. in fifteen days.

Clinical Diagnosis. (1) Multiple arthritis; (2) prostatitis and seminal vesiculitis; (3) chronic urethritis.

CASE XIX.—H. M., male, aged fifty-two years, was admitted to hospital May 9, 1922, complaining of pain in back and legs.

Present Illness. Well until one year ago, when he began to have pain in back and legs, this condition while persistent at all times since then became very severe on several occasions, forcing patient to remain in bed. On admission temperature 98° F., pulse 80.

Treatment. Tolysin 1 gm. three times a day for six days without appreciable relief.

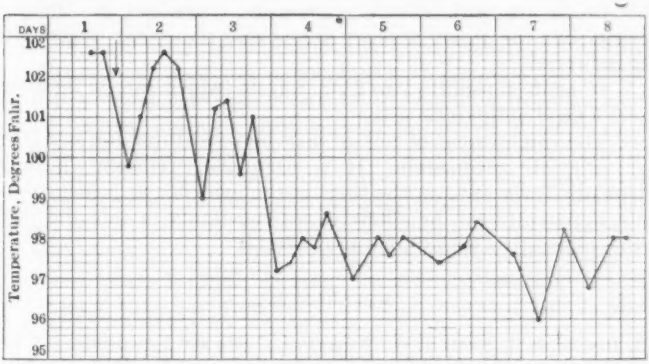

FIG. 4.—Acute tonsillitis. Readings every four hours. Tolysin 1.3 gm. every two hours, then 1.3 gm. every four hours, started at arrow.

3. FURTHER OBSERVATIONS ON TOLYSIN AS AN ANTIPYRETIC AND ANALGESIC. Tolysin has been further studied in 3 cases of

acute tonsillitis, 4 of ordinary "cold," and upward of 15 headaches, types of cases in which antipyretics, especially aspirin are generally used. As an analgesic for the relief of headache tolysin requires somewhat longer to act than do the salicylates. Doses of 0.7 to 1.0 gm. were usually found effective. The malaise and fever associated with the onset of a "cold" were relieved by tolysin in doses of 0.7 to 1.0 gm. every three hours for 2 or 3 doses. In the 3 cases of acute tonsillitis tolysin proved an efficient antipyretic in doses of 1 to 2 gm. repeated every three or four hours.

Temperature Chart IV is the fever record of a case of acute tonsillitis, showing the action of tolysin.

Summary. 1. Tolysin (ethyl ester of paramethylphenylcinchoninic acid) appears to be a very safe drug.

Two different patients received each 50 gm. of tolysin within eight days without any untoward symptoms whatever. Our recent laboratory investigation has shown that the body is unable to absorb much more than the therapeutic dose.

2. In a series of 12 cases of acute rheumatic fever tolysin was found a fully efficient therapeutic agent. The usual dose required for complete relief of symptoms is 10 to 16 gm. Partial relief was obtained with 7 to 8 gm. A satisfactory routine is to give 2 gm. every two hours for 3 doses, followed by 2 gm. every four hours. No gastric symptoms were elicited, and albuminuria was increased in only one case.

3. Satisfactory results were further obtained in 6 out of 7 cases of arthritis of other types, including acute infections and chronic joint pains.

4. Tolysin has been employed in cases of ordinary "colds" and headaches with effects apparently equivalent to those of aspirin, but the action appears slower and somewhat larger doses are indicated.

5. In acute tonsillitis 1 to 2 gm. tolysin (which can be repeated) exert a good antipyretic action.

6. The employment of tolysin may be substituted for any internal salicylate medication. It is particularly efficient in acute rheumatic fever and, on the basis of the evidence at present available, apparently can be administered constantly in this and other forms of arthritis without harmful effects.

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THE EARLY SYMPTOMS AND THE DIAGNOSIS OF TUMORS OF THE SPINAL CORD, WITH REMARKS ON THE SURGICAL TREATMENT.*

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In the progress of our understanding of disease, as in the story of the forward march of other branches of human knowledge, history repeats itself. Symptoms were again and again described as a disease but were found to be only a result or a symptom. The diagnosis "primary peritonitis" became more and more rare with the advances in our knowledge of the pathology of the intra-abdominal organs. We are beginning to realize that primary inflammations of the pleural membranes are unusual and that the pleural lesion is most often secondary to a pathological process in the cortical portions of the lungs. Who knows but that meningitis will one day be shown to hold the same relation to affections of the brain and spinal cord that peritonitis does to the abdominal viscera and inflammation of the pleura to the lungs.

Not so many years ago "chronic transverse myelitis" was considered a disease of frequent occurrence; we now know that it is rare. That this supposed affection has been relegated to the background of the past is mainly due to the advances in our knowledge of local spinal compression, and more especially to our understanding of the pathological effects and the symptoms of tumors of the spinal cord.

The history of the marvellous progress made in this field is one that must deeply impress the student of the subject. In 1882, a great clinician made the statement that "the existence of an intraspinal tumor can hardly be determined with certainty, and, assuming that a tumor exists, to determine its character from the symptoms is impracticable."[1] And a surgeon, famous in his day, had declared that "the operation of trephining the spine is an operation not within the range of practical surgery."[2] At the same period, however, Gowers, Leyden, Erb and Osler voiced the belief that tumors of the cord could be recognized and were, perhaps, amenable to surgical treatment. How quickly was the darkness and doubt dispelled when, in 1887, Horsley successfully removed a spinal cord tumor that has been correctly diagnosticated and localized by Gowers.

In the thirty-five years that have passed since Horsley and

* Read before the Section of Neurology at the Stated Meeting of the New York Academy of Medicine, March 16, 1922.

[1] Flint, Austin: Practice of Medicine, 1882.

[2] Heath: History of Surgery, 1881.

Gowers' epoch-making operation[3] our knowledge of the symptomatology of spinal tumors and of their surgical treatment has made rapid strides. Then, the neurologist was victorious if he successfully determined the level of a spinal new growth. Now, we are able to diagnose from the progress of the symptoms and the signs of interference with function—not only the level of the cord lesion, but also the location of the growth in relation to the cord, the ventral and dorsal roots, and the dentate ligament. Then, spinal tumors were considered very rare; now, they are met with frequency. Then, the symptomatology was considered invariable—a beginning with root pains and a progress with increasing sensory and motor paralysis. Now, we know that many cases begin without pain and progress with irregular motor and sensory disturbances. Then, a diagnosis could be made only when the signs of motor and sensory loss were far advanced. Now, we can often make the diagnosis before much paralysis or sensory disturbance has occurred if the patient comes under observation early enough. Then, the operation of laminectomy was a hazardous procedure; now, the exposure and removal of a spinal neoplasm is an operation devoid of great danger.

The story of the stages in the progress is of absorbing interest. As the time is short, I can only speak of some aspects of the subject, and have selected the subject of the early symptoms of spinal cord tumors.

Pain and Other Subjective Sensory Disturbances as Early Symptoms. As our understanding of pain due to irritation of sensory spinal roots became greater, we began to have a fuller realization of the significance of this symptom. At the present time the very word neuralgia, if the cranial nerves are excepted, should bring to the mind of the physician the possibility of a root pain. This subject is not only of importance to the neurologist and the neurological surgeon, but also to the general practitioner and the general surgeon. Many patients with spinal cord tumors have a long period lasting from many months to five or even eight years, during which they complain of pain in one or other part of the body, due to irritation of one or more sensitive posterior roots. These patients are treated for long periods for neuralgia. If the pain affects an upper extremity, it is considered a brachial neuritis, if in the thorax it is called intercostal neuralgia or perhaps pleurisy; if the lower extremities are affected, the cases are called sciatica. When these painful symptoms occur in the abdomen, an intra-abdominal lesion is thought of and only too often an abdominal operation of one kind or another performed. I am repeatedly seeing patients with disease of the thoracic cord who have had

[3] No one who is interested in spinal-cord tumors should fail to read the original report of the case. It was published in the Medico-Chirurgical Transactions, London, 1888.

one or more laparotomies or other operations for supposed abdominal or pelvic disease.

The following are a few cases of this nature:

CASE I.—Mrs. W. (Neurological Institute, 1916). In 1910, the patient complained of sciatica and was treated for it. As she had large hemorrhoids, these were supposed to be the cause and the hemorrhoids were removed by a surgeon. The symptoms continued and there were added pains in the lower portion of her back and extending into the rectum. As she had a movable coccyx, this was removed in 1911. In 1912, the sphincter ani was stretched and partly cut. In 1913, a sigmoidopexy was done. In 1914, a ventral suspension was done. But none of these operations relieved the symptoms. The patient became more and more miserable, complaining constantly of a sensation of pressure in the rectum with continual desire to move her bowels, pain high up in the rectum and in the bladder and pain in the lower portion of her back. She noticed that when she took a cathartic, she sometimes did not have perfect control of her bowels and occasionally of her bladder. There were no disturbances in the lower extremities. Finally, a lumbar puncture was done and yellow fluid was withdrawn under pressure, and then neurological examination revealed that there were very slight sensory disturbances over the lower sacral areas. At the operation a small tumor, about the size of an almond, was removed from between the roots of the cauda equina.

CASE II.—Samuel T. (Neurological Institute No. 12,955). Four years previously the patient suffered from rheumatism in both legs. For one year he noticed that sneezing caused him severe pain in the rectum. At the same time he began to have difficulty in passing his water. He was told that he had a slight amount of cystitis, a small amount of residual urine and a markedly large prostate and he was advised to have his prostate removed. Before subjecting himself to this operation, examination showed that the lower abdominal reflexes were weak, that the ankle jerks were slightly exaggerated and that there were very slight sensory disturbances. A lumbar puncture was then done and the typical fluid of spinal cord tumor found. At the operation, a tumor about the size of a small olive was removed, lying in front of the cord at the level of the tenth thoracic segment.

CASE III.—Mrs. B. (Mount Sinai Hospital No. 173,333). Two years' history of pain in the right hypochrondrium and right side of the abdomen. Cholecystectomy, later appendectomy; no relief. Finally, spinal symptoms discovered. Laminectomy and removal of lobulated tumor from underneath the sixth, seventh, and eight thoracic spinal roots on the right side.

CASE IV.—Alexander B. (Mount Sinai Hospital No. 214,385). Twenty-one months' history of attacks of pain in the left hypochondrium and left lumbar region, usually worse after meals. After thirteen months, tingling in the soles of both feet and slight weakness. Five months before admission, laparotomy for suspected gastric ulcer. November 22, 1921: laminectomy and removal of spinal cord tumor from the anterior and left side of the cord at the seventh thoracic segment.

Instead of beginning with neuralgic pain, some patients first complain of a persistent pain in the back of the neck or in the thoracic spine. The pain is usually strictly localized and does not radiate for a long time. Later it may radiate around the body or down one or both limbs. The pain is very similar to that of malignant disease of the vertebræ, but the pain of malignant disease is more apt to be felt in front of the chest as well as in the back and is more often made worse by movement. On the other hand, patients with extramedullary spinal tumors often state that the pain in the back is made worse by coughing or by sneezing. In not a few of these patients, the roentgen-ray picture shows more or less marked arthritis of the vertebræ and the roentgen-ray changes may be so marked that the patient is actually treated for Pott's disease. In the early stages, it is often difficult to differentiate the pain in the back from that which occurs in primary or secondary vertebral disease or from aneurysm of the aorta. For a long time the symptoms may be perplexing. In every patient who complains of persistent pain in the back, repeated neurological examinations should be made.

Pain in the lower part of the back is one of the earliest and most continuous symptoms of the large intradural tumors of the lumbosacral parts of the cord and of the roots of the cauda equina. This "pain in the small of the back" is usually made worse by movement and by coughing and sneezing, and may for years be the only symptom. The pain is either continuous or occurs in attacks and the patients are supposed to be suffering from lumbago. After a period of, perhaps, years, the knee jerks are found to have been lost, and then the diagnosis of locomotor ataxia may be made. Finally, the characteristic symptoms and signs of conus or cauda become evident.

The late Dr. Pearce Bailey was one of the first to call attention to the fact that in a certain number of instances, spinal cord tumors develop without any painful symptoms. These cases are of sufficient frequency to demand consideration. It has been my experience that tumors with a painless onset occur either with a growth of small size which has developed from the pia or arachnoid on the anterior or antero-lateral aspect or on the posterolateral

surface of the cord between two nerve roots. In these patients, root symptoms may appear late instead of early in the disease.

Bailey was correct in his statement that there is a group of spinal cord tumors which begin without pain. Dr. Stookey and I, studying my spinal tumor records, have found that the large majority of cases of spinal tumor have some kind of subjective sensory disturbance as an early symptom. The accompanying table (see Table I) gives the early sensory complaints in the patients.

TABLE I.—SENSORY SYMPTOMS AT ONSET.

	Extra-medullary.	Extra-dural.	Conus and cauda.	Intra-medullary.
Root pains	19	3	0	2
Pain in back or in neck	6	4	1	4
Pain in back extending down limbs	1	2	7	0
Pain in homolateral limb below level	1	1	0	0
Pain in contralateral limb below level	2	1	0	0
Pain in both legs below level	2	0	2	0
Pain in rectum	1	0	1	0
Pain in chest or abdomen	2	2	0	1
Tingling, burning, heaviness, pin-and needle sensation or numbness of homolateral limb below level	1	0	0	4
Tingling, burning, heaviness, pin-and-needle sensation or numbness of contralateral limb below level	5	0	0	0
Tingling or numbness of both lower limbs	3	0	0	2
Tingling without pain, on same side	1	0	0	0
Tingling without pain, on opposite side	2	0	0	0
Numbness or heaviness, but no pain	1	1	0	0
Feeling of stiffness, but no pain	1	0	0	0
No sensory symptoms	1	0	2	2

A number of different sensations are recorded as early symptoms. Many complained of a pain that was evidently radicular in character; others of a localized or radiating pain in the back, others of a visceral pain. Tingling, burning, heaviness, numbness, stiffness or a "pin- and needle" sensation, were very often complained of. Total absence of complaints regarding some kind of abnormal sensation was very rare in extramedullary and extradural growths, and was somewhat more frequent in intramedullary growths. It is especially noteworthy that a considerable number of patients with extramedullary tumors complained of paresthesiæ of some kind—a symptom which was once considered characteristic of intramedullary growths.

Diminution or loss of articular sense, which is seen whenever one or both posterior columns are involved, was never recognized as such by the patients; they are apt to interpret the disturbance as a motor weakness. In not a few instances the patients stated positively that one limb was much weaker than the other, although the examination showed that there was no loss of motor power but only loss of the sense of position of the affected limb.

Early Subjective Motor Disturbances. In the majority of the patients, the motor disturbance that is first noticed by the patient occurs in the upper or lower extremity on the side of the tumor. If the growth is situated in the lower cervical (C VI—C VIII) and upper thoracic segments, the sequence of the limbs is usually (1) homolateral upper extremity, (2) homolateral lower extremity, (3) contralateral lower, and (4) contralateral upper extremity. Sometimes, however, the contralateral upper limb is affected before the lower limbs, and sometimes weakness of the contralateral lower limb is noted before the homolateral one.

In order to understand the apparently paradoxical weakness of the limb on the side opposite to that of the tumor, the mobility of the cord and the mechanical effects produced by spinal new-growths should be thoroughly understood.

In extradural and intradural growths which are adherent to the dura, the cord is often pushed to the opposite side of the dural sac by the fluid between the cord and the growth. When this occurs there is a period during which the side of the cord opposite to that of the tumor is pressed against the dural sac and the bony wall of the spinal canal. As a result, contralateral motor symptoms may be observed, and on examination the contralateral limb may be weak and spastic and the reflexes on that side exaggerated as the result of the compression of that side of the cord against the dura and bone wall of the vertebral canal.

Early Objective Sensory Disturbances. The mobility of many segments of the spinal cord is such that sensory disturbances may also occur as the result of the mechanism above described. Unless correctly evaluated, these sensory disturbances may lead to an incorrect localization of the tumor in relation to the cord. In tumors adherent to the dura (both extradural and intradural) there is often a stage during which the sensory disturbances (especially as regards pain and temperature) are more marked on the side of the tumor while the motor signs are most distinct on the opposite side. We have become accustomed to call this clinical picture a "reverse Brown-Séquard." Similarly we have seen early posterior column disturbances with tumors on the ventral aspect of the cord, from the backward dislocation of the affected part of the cord and the impact of the posterior column against the bony walls of the spinal canal. The reasons why these disturbances have not been more often observed, is that the patients are not more often seen by a neurologist in the earliest stages of spinal compression.

In extramedullary tumors of the spinal cord, the earliest evidence of diminution of superficial sensibility is to be found either over root areas at the level of the growth or in the peripheral parts of the limbs. Sensory disturbance in the toes or fingers should be carefully looked for in early suspected spinal disease. It is especially apt to occur in tumors on the posterior or postero-lateral

aspect of the cord, and is more rare in anterior growths. In the latter, as well as in intramedullary tumors, the earliest and most marked sensory disturbance involves the dermatomes just below the segmentary cord level.

The Diagnosis of the Location of Tumors in Relation to the Cord. It is no longer sufficient to make a diagnosis of an extramedullary tumor at one or another level of the cord; we must now diagnose the exact relation of the tumor to the cord. In order to make this more precise localization, a general plan of classification of the relations of such growths is necessary.

We are accustomed to classify tumors, in their relation to the cord, in the following manner: Tumors behind the posterior roots we call posterior; those between the posterior roots and the dentate ligament are postero-lateral; those between the dentate and the anterior roots are antero-lateral; finally, those in front of the anterior roots are anterior growths.

The following two tables (Tables II and III) give the segmentary level and the local relations of the growths in our patients. In the second table (Table III) the tumors of the conus and cauda equina are not included because these tumors usually surround and lie between the caudal roots and exact classification as to their relation to the structures is not possible. This second table shows that in our experience 62 per cent of the extramedullary growths lie, according to our method of classification, on the posterior or postero-lateral aspect of the cord, while 36 per cent lie anterior or antero-lateral. This high relative proportion of ventral or ventro-lateral growths is of considerable importance because it is the growths in these locations that often give indefinite symptoms and signs for a considerable period of time.

TABLE II.—SEGMENT LEVEL OF TUMORS.

	Extramedullary.	Extradural.	Intramedullary.
Cervical—1–4	3	0	0
4–8	11	4	8
Thoracic—1–4	7	2	2
4–8	10	5	2
8–12	9	2	3
Lumbosacral and cauda	15	0	0
Totals	55	13	15

TABLE III.—RELATION OF TUMORS TO SURFACES OF CORD.

	Extramedullary. (Not including conus and cauda.)	Extradural.
Anterior and median	1	1
Anterior and lateral	6	4
Antero-lateral	6	2
Posterior and median	2	0
Posterior and lateral	12	2
Postero-lateral	14	3
Lateral and posterior	1	0
Anterior and posterior	0	1
	42	13

Posterior tumors are characterized, above all, by root pains and by very marked posterior column disturbances. In growths on the dorso-lateral side of the cord, the root pains are apt to be very severe, and the Brown-Séquard type is apt to be very distinct. If a suspected spinal tumor causes root signs on one side of the body, sensory disturbances on the same side, and motor disturbances on the opposite side of the body (excluding, of course, tumors between the roots of the cauda equina) there is considerable probability that the tumor is either extradural or intradural and primarily from the dura itself.

Growths on the ventro-lateral aspect are apt to have a beginning without root pains with a Brown-Séquard picture and early local muscle atrophies. Growths in this location may also give signs of a reversed Brown-Séquard picture, and in such instances, also, the diagnosis of a dural origin is probable.[4]

Tumors on the anterior aspect of the cord very frequently have a painless beginning, with tingling in one or both lower limbs and relatively late sensory disturbances.

If we exclude root signs, hyperesthesia and diminution of sensation, there is no doubt that in a large number of the patients, if seen early enough, the first objective sensory disturbances will be found in the most peripheral part of the lower extremities in posterior or postero-lateral growths, and over the trunk in anterior or antero-lateral tumors. A sensory disturbance, most marked near the level of the spinal lesion, is characteristic also of intramedullary growths, but in these patients a Brown-Séquard syndrome or even an indication of this clinical picture is rare. We have not, I believe, paid sufficient attention to this subject and have not, in suspected spinal tumors, made a thorough search for the slightest evidence of diminution of sensation in the peripheral parts of the lower extremities.

In direct contradiction to the belief which is general and which is to the effect that there is no arrangement of fibers in the tracts of the cord corresponding to extremities and to different parts of the extremities—a belief which for many years has been grounded on clinical and pathological evidence—I have become convinced that there is a grouping of fibers for the different parts of the body in most if not all of the pathways of the cord. It is only on such a basis that it is possible to explain the not infrequent occurrence of motor and sensory disturbances in the lower limbs as the earliest signs and symptoms of extremedullary cord tumors in the cervical region.

If all the facts to which attention has been called in the foregoing remarks are taken into account, they will be found to aid

[4] This subject is of considerable diagnostic importance, and we shall, in another paper, discuss the mechanical effects of spinal-cord tumors and the resulting variations in the symptomatology.

in the differentiation between extramedullary and intramedullary, and also between extradural and intradural growths.

From the surgical standpoint, the finer localization of a tumor with reference to the cord is of importance, for it will allow the surgeon to plan and execute his operation in accordance with the conditions that exist. Thus, if a tumor is supposed to lie on the anterior aspect of the cord and more to one side, more of the laminæ on that side will have to be removed in order to gain the best access to the front of the spinal cord, and the number of vertebral arches to be at first removed will have to be larger, as it is probable that the cord will have to be dislocated in order to expose and remove the tumor.

If, on the other hand, the growth lies on the posterior aspect of the cord, the number of vertebral arches and the amount of each arch that is removed in the laminectomy may be reduced to the minimum.

LARYNGEAL PARALYSIS ASSOCIATED WITH THE JUGULAR FORAMEN SYNDROME AND OTHER SYNDROMES.*

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Complete unilateral paralysis of the recurrent laryngeal nerve is not uncommon and is usually due to aortic aneurysm, carcinoma of the esophagus, or pressure on the nerve from some type of neoplasm.

Jackson, in 1864, first described complete unilateral laryngeal paralysis associated with paralysis of the soft palate, tongue, trapezius and the sternocleidomastoid muscles. Since the lesion occurs in the region of the jugular foramen where the ninth, tenth, and eleventh cranial nerves leave the skull and the hypoglossal foramen, through which the hypoglossal nerve passes, the syndrome has been called the jugular foramen syndrome of Jackson. Jackson's original description does not contain details with regard to the involvement of the ninth cranial nerve, as shown by the change in the sensation of taste on the posterior part of the tongue and by involvement of the pharynx.

Mackenzie, in 1883, reported a patient with a syphilitic lesion of, or near the medulla causing paralysis of the soft palate, tongue, vocal cord, and the sternocleidomastoid and trapezius muscles. The patient did not respond to treatment for syphilis. He had constant headache and vomited occasionally. A swelling of nine

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months' duration involved the left side of the soft palate and the tonsil, and displaced the uvula to the right. It is possible that this patient had a nasopharyngeal tumor with secondary affection of the jugular foramen and intracranial involvement. Mackenzie, in discussing Jackson's case, at the Harvaine Society, in 1886, said that he had seen 8 patients with unilateral paralysis of the tongue, soft palate, and vocal cords.

Collet, in 1915, reported a case of what he called, "The total syndrome," in which the ninth, eleventh, and twelfth cranial nerves were affected. The patient was a soldier who had received a bullet wound in the right mastoid region. He complained of difficulty in swallowing, deafness, and noises in the ear. The roentgen-ray showed a shrapnel ball situated at the base of the skull. There was hemiplegia of the tongue, larynx, palate, and pharynx and of the sternocleidomastoid and trapezius muscles, and lack of perception of taste at the base of the tongue on the side involved.

Avellis, Schmidt, and Tapia have reported syndromes associated with laryngeal paralysis in which certain variations have occurred. Avellis reported paralysis of the tenth cranial nerve, Schmidt of the tenth and eleventh nerves, and Tapia of the eleventh and twelfth.

Lannois and Vernet reported 2 cases of war wounds; in 1 the bullet entered the malar region and in the other it entered the preauricular region. In both cases the ninth, tenth, eleventh, and twelfth nerves were affected, and in the second case the cervical sympathetic as well.

Lannois and Jouty reported a case of a soldier injured back of the angle of the jaw; the last four cranial nerves were affected. These authors found that 17 instances of the jugular foramen syndrome had been reported.

Vernet reported a case in which a soldier was injured by a shell fragment passing through the external auditory canal. Roentgenograms revealed the fragment in the prevertebral region. Besides the total syndrome the seventh nerve on the injured side was paralyzed by the wound.

Hall, in a consideration of the etiology of unilateral paralysis of the recurrent laryngeal nerve, collected 116 cases and found that in 10, besides the laryngeal paralysis, there was hemiplegia, paralysis of the face, palate, pharynx, and trapezius and sternocleidomastoid muscles.

Thomson, in an analysis of the 360 cases of unilateral paralysis of the larynx, found 1 in which symptoms were due to an extracranial growth close to the exit of the vagus.

Guder and Dufour reported 63 cases of unilateral paralysis of the recurrent laryngeal nerve, but none were associated with the jugular foramen syndrome.

Aloin reported a case of acute phlegmon of the pharynx and neck;

the patient developed paralysis of the soft palate, vocal cord and tongue with weakening of the shoulder muscles due to neuritis of the tenth, eleventh, and twelfth cranial nerves. He noted that involvement of the tenth nerve was shown by intense salivation, pulse 140, and difficulty in breathing not accounted for by any mechanical cause. Several months passed before the paralyzed muscles returned to normal.

Cauzard and Laignel-Levastine reported a syphilitic lesion of the right bulb with involvement of the fifth, seventh, ninth, tenth, eleventh and twelfth cranial nerves.

Beck and Hassin reported a case of tuberculosis of the cervical glands and secondary invasion of the ninth, tenth, eleventh, and twelfth nerves. The symptoms improved markedly following removal of the glands. The symptoms recurred, and a second operation was performed to free the nerve from the scar tissue.

Pollock reported a similar case in a man in whom the last four cranial nerves and cervical sympathetic nerves were affected owing to tuberculous adenitis. There was no change in pulse, respiration, secretion or sensation.

It is seen that many varieties of symptoms may result from involvement of the last four cranial nerves in the region of the jugular foramen.

Lannois and Bourcart reported the involvement of the cervical sympathetic nerve associated with laryngeal paralysis.

TABLE I.—SUMMARY OF CASES.

Case.	Age, sex.	Duration.	Cause.	Primary nasopharyngeal tumor.	Secondary nasopharyngeal tumor.	Cranial nerves.										Cervical sympathetic nerve.
						Second.	Third.	Fourth.	Fifth.	Sixth.	Seventh.	Ninth.	Tenth.	Eleventh.	Twelfth.	
A81249	62 F.	3 years	Indeterminate, neoplasm (?)	....	..	..	..	..	..	..	..	..	+	+	+	
A165869	52 M.	8 years	Epithelioma	....	+	..	+	+	+	+	+	+ (?)	+	+	+	
A271166	47 M.	6 weeks	Neoplasm (lymphosarcoma?)	+ and pharynx	..	..	..	..	..	..	..	+ (?)	+	+	+	+
A285410	35 M.	2 years	Carcinoma (mixed tumor type)	....	..	..	..	..	..	..	..	+	+	+	+	+
A348444	43 F.	12 years	Neoplasm (mixed tumor type?)	....	..	..	..	..	..	..	..	+	+	..	+	+
A350568	54 F.	3 months	Neoplasm (lymphosarcoma?)	+	..	+	+	+	+	+	..	+	+	+	+	+ (larynx not involved).
A361632	40 F.	4 years	Neoplasm (mixed tumor type?)	....	..	..	..	..	..	..	..	+	+	+	+	

Vernet gives a complete table showing the effect of paralysis of the ninth, tenth, eleventh, and the twelfth cranial nerves. What he considers the internal branch of the eleventh nerve is usually classified in this country as part of the tenth. This, however, is a matter of nomenclature. The distribution of the ninth and tenth nerves, as seen in Table II, is not absolute. The affection of the cervical sympathetic nerve is shown by myosis, narrowing of the palpebral fissure, and enophthalmos.

TABLE II.—PARALYSIS OF THE LAST FOUR CRANIAL NERVES.

	Vernet.	Oppenheim.
Paralysis of the ninth	Paralysis of the superior constrictor of the pharynx (curtain movement of the posterior wall, disturbances in deglutition of solids). Disorders in taste, posterior one-third of tongue.	Loss of taste over the posterior part of the tongue. Difficulty in swallowing owing to paralysis of some of the pharyngeal muscles. Abolition of reflex excitability of the pharyngeal mucosa.
Paralysis of the tenth.	Disorders in sensibility of half of the soft palate, of the pharynx, of the larynx and of the auricular branch. Disorders of salivation. Coughing crises. Disorders of respiration (intermittent dyspnea and pseudo-asthma).	Unilateral paralysis of the palate, pharynx and larynx. Anesthesia of the pharynx, larynx and external auditory meatus, rarely found. Sometimes slowing, sometimes acceleration (irregularity) of breathing. Heart symptoms not constant, sometimes slowing but most often accelerated.
Paralysis of the eleventh internal branch. Paralysis of the eleventh external branch.	Paralysis of half of the soft palate and larynx. Acceleration of the pulse. Paralysis of the sternocleidomastoid and trapezius muscles.	Paralysis of the sternocleidomastoid and trapezius muscles.
Paralysis of the twelfth.	Hemiparesis of the tongue.	Hemiparesis of the tongue.

Report of Seven Cases Observed in the Mayo Clinic. CASE I (A81249).—Mrs. T. J. D., aged sixty-two years, came to the Clinic, June 29, 1921. She had had two operations for exophthalmic goiter, February 3, 1914, and January 6, 1915, respectively. For the last two or three years she had noticed shrinking and weakness of the right side of the tongue. The last nine months she had had hoarseness, and breaking of the voice, difficulty in swallowing, regurgitation of food, breathlessness on exertion, and pronounced tachycardia and palpitation. She had had pain in the left arm for three or four months.

Examination revealed the middle line of the palate displaced to the left, and partial paralysis of the right side of the palate. The right side of the tongue was atrophied and protruded to the right. The right vocal cord was fixed in the intermediate or cadaveric

position. No pathological changes were demonstrable in the nasopharynx, nor was change in sensation demonstrable in the pharynx or larynx. The right sternocleidomastoid and trapezius muscles were partially paralyzed and atrophied.

Summary. In this case the tenth, eleventh, and twelfth nerves on the right side were affected partially. The etiological factor was questionable but the condition was probably due to a neoplasm in the region of the jugular foramen.

CASE II (A165869).—Mr. H. N., aged fifty-two years, came to the Clinic, July 13, 1921, because of recurring epithelioma of the right cheek. He had had syphilis thirty years before. When a child he had been injured on the right cheek at the site of the present lesion. The area had remained discolored until twelve years before when a sore had developed. In 1918, this area was plastered by a cancer quack and, in 1920, it was excised. Roentgen-ray treatments had been carried out four months before; the cheek had been cauterized and medicinal treatment given by the local physician one week before.

Examination showed a recently cauterized opening in the right cheek just below the malar bone, 3.75 cm. in diameter and 2.5 cm. deep. A specimen removed from the margin revealed basal-cell epithelioma. The Wassermann reaction was strongly positive, amounting to total inhibition.

July 20, 1916, the area on the right cheek was thoroughly cauterized with soldering irons and treatment for syphilis instituted.

The patient returned June 6, 1919, complaining of diplopia and pain over the right side of the head. Examination showed paralysis of the right external rectus muscle and involvement of the fifth nerve. August 8, 1919, almost complete paralysis of the right fourth, fifth, and sixth nerves had developed.

February 24, 1921, the patient returned and requested a plastic closure of the opening in the right cheek, about 5 cm. in diameter, which connected the nose, the antrum, and the mouth. Since our last examination, August 1919, two operations had been done elsewhere, one, fifteen months before, and one, twelve months before. The right eye had been removed with the orbital growth and a plastic operation attempted. Examination then showed a recurring basal-cell epithelioma at the right margin of the orbit. The left eye was normal, the fundus negative, and vision 6/6. There was a definite fulness in the right nasopharynx. The small recurrent growth was removed and treatment for syphilis was given.

December 27, 1921, the patient returned complaining of pain on the right side of the head, hoarseness, and difficulty in swallowing. The right side of the soft palate and pharynx was paralyzed and the right cord was fixed in a cadaveric position. There was diminished sensation over the right side of the pharynx and a collection

of mucus in the hypopharynx. There was paralysis of the right sternocleidomastoid and trapezius muscles. The right nasopharynx was filled with a sloughing area, malignant in appearance. The patient was deaf in the right ear owing to involvement of the nasopharynx. There was complete facial paralysis on the right with areas of anesthesia on the affected side.

Roentgenograms of the skull were negative; examination of the left fundus was negative. The pulse was 88, and there was no respiratory trouble. Examination showed involvement of the fifth, seventh, ninth, tenth, eleventh, and twelfth cranial nerves.

Summary. The right third, fourth, fifth, sixth, seventh, ninth (?), tenth, eleventh, and twelfth cranial nerves were affected owing to direct extension from an epithelioma of the cheek to the region of the jugular foramen and possible extension intracranially.

Case III (A281166). Mr. M. F. M., aged forty-seven years, came to the Clinic, February 2, 1921. Six weeks before, the patient had had pain over the right mastoid region and had noticed something wrong with his throat which seemed sore. His home physician had lanced it, expecting to find an abscess, but no pus was found. Pain in the right ear had been accompanied by slight deafness. The patient had been unable to swallow for a week, as fluids strangled him and regurgitated into his nose. He had lost 17 pounds in the last six weeks.

Examination showed drooping of the right upper eyelid and a small right pupil. A non-ulcerating mass in the right side of the nasopharynx extended into the pharynx and partially into the hypopharynx. Metastatic glands were present at the right angle of the jaw. The muscles on the right side of the palate were paralyzed. There was a great deal of mucus in the right pyriform fossa and the right cord was fixed in the intermediate or cadaveric position. The right side of the larynx was somewhat insensitive and paralysis of the muscles of the right side of the pharynx and of the sternocleidomastoid and trapezius muscles was noted. The tongue protruded to the right. There were no respiratory or cardiac disorders. The ninth, tenth, eleventh, and twelfth nerves were affected by the nasopharyngeal and the pharyngeal tumor.

Summary. This patient presented a rapidly growing tumor, probably lymphosarcoma, of the right nasopharynx and pharynx, and affecting the ninth (?), tenth, eleventh, and twelfth nerves and the cervical sympathetic nerve.

Case IV (A285410).—Mr. A. W., aged thirty-five years, came to the Clinic, August 29, 1919, on account of roaring and pain in the right ear of two years' duration. A year before he had become deaf. Since then he had had attacks of sharp pains in the right ear which had lasted only a few minutes. There was no discharge from the

ear, but about one year ago a small tumor had appeared below it. The patient's general health was good.

Examination revealed a small, rounded, pedunculated tumor on the floor of the right auditory canal, 1.5 mm. in diameter, and a tumor in the right parotid region just posterior to the ascending ramus of the jaw, which was about 3.75 cm. in diameter and "felt" malignant. The tumor in the auditory canal was removed, but malignancy was not demonstrable microscopically. The ear drum was normal. A roentgenogram of the skull was negative and the neurological examination afforded nothing of note. September 3, 1919, the mass in the parotid region was explored by Dr. Sistrunk, but the tissue removed did not show malignancy.

The patient returned October 21, 1920, complaining of loss in weight, hoarseness, and difficulty in swallowing of eight weeks' duration. He had pain lasting for a few minutes at a time in the right shoulder and right side of the neck. The right cord was fixed in the cadaveric position with a collection of mucus in the pyriform fossa. Paralysis of the soft palate, pharynx, and vocal cord was complete on the right side. Neither edema nor neoplasm was visible. The tumor below the right ear in the parotid region was still present. The sternocleidomastoid and trapezius muscles were partially paralyzed.

The ninth, tenth, eleventh, and twelfth cranial nerves were affected, due to a tumor arising in the right parotid region and extending to the jugular foramen.

November 13, 1920, Dr. Adson explored the area and found a carcinoma of the mixed-tumor type, 3 cm. in diameter and 17.5 cm. in length, situated in the region of the jugular foramen outside of the skull with some extension into the cranial cavity through the foramen. The tumor was removed. The patient recovered uneventfully, but with no change in the nerve, as had been expected.

Summary. In this case the tumor was a carcinoma of the mixed-tumor type in the right parotid region. The carcinoma involved the jugular foramen extracranially, and the ninth, tenth, eleventh, and twelfth cranial nerves.

Case V (A348444).—Mrs. W. B., aged forty-two years, came to the Clinic, February 3, 1921. She complained of weakness, hoarseness, choking sensation, and drooping of the right eyelid of about two years' duration. When swallowing, she had noticed a choking sensation in the throat, and coughing had brought food back into her mouth. Sixteen months before, she had noticed that the right side of her tongue was thick and stiff. When eating she had perspired freely over the right side of the face and scalp so that drops of water fell to her shoulder. Her heart had palpitated at times and she had become dyspneic when climbing stairs. She had lost 32 pounds in weight, 10 during the last month.

Examination revealed a very slight ptosis of the right upper eyelid; the right pupil was myotic. Vision was normal. Examination of the nasopharynx was negative. The right half of the tongue, the right side of the soft palate, and all of the pharyngeal muscles were paralyzed and atrophied. The right vocal cord was fixed in an intermediate position. There was marked anesthesia over the soft palate, the right pharynx, and the larynx. The sternocleidomastoid and trapezius muscles were not paralyzed. A firm mass 3.5 cm. in diameter was found between the right angle of the jaw and the mastoid process. Examination of the heart revealed a loud systolic murmur, heard best at the apex and transmitted to the axilla. Anemia was marked. The hemoglobin was 30 per cent, the erythrocytes numbered 3,170,000 and the leukocytes 5800. The color index was 0.4; polynuclear neutrophils, 67.5; small lymphocytes, 27.5; large lymphocytes, 4.5; basophils, 0.5; anisocytosis and poikilocytosis were slight.

Summary. This case illustrates involvement of the ninth, tenth, and twelfth cranial nerves and possibly partial involvement of the cervical sympathetic nerve by a mixed tumor in the region of of the jugular foramen.

Case VI (A350568).—Mrs. F. O. B., aged fifty-four years, came to the Clinic, February 25, 1921. Three months before, she had noticed pain above and behind the right eye and deafness in the right ear. Two months before, she had had difficulty in opening the mouth wide, a swelling had appeared on the right side of the face, and the right nostril had become obstructed. Three weeks before, the corner of the mouth and the upper eyelid on the right side had begun to droop. Two weeks before, she had noticed that she could not move the right eye; it became more prominent, and blindness developed gradually.

The general examination showed nothing of note. Examination of the eyes revealed a proptosis of the right with drooping of the upper eyelid, complete ophthalmoplegia, and blurring of the disc. Pupillary reflexes were absent; the right pupil was dilated. Vision of the right eye was 0, of the left 6/4. There was bulging of the right temporal region. A tumor, ulcerated and bulging to the middle line, filled the right side of the nasopharynx. The Eustachian tube could not be seen. The right side of the palate and pharynx was paralyzed. The tongue deviated to the right. There was no laryngeal paralysis. Sensation was decreased over the right cheek, the forehead and chin, and the action of the muscles of mastication was impaired. The trapezius and the sternocleidomastoid muscles were not paralyzed. Deafness was complete in the right ear.

Summary. This case illustrates involvement of the third, fourth, fifth, sixth, ninth, tenth, and twelfth cranial nerves and probably

the cervical sympathetic nerve by a rapidly growing nasopharyngeal tumor, probably lymphosarcoma. The deafness was owing to encroachment of the tumor on the Eustachian tube.

CASE VII (A361362).—Mrs. G. L., aged forty years, came to the Clinic, June 15, 1921. Seven years before, following childbirth, the patient had noticed difficulty in swallowing. Three years later, she had become suddenly hoarse; this persisted. She had not coughed, but in swallowing she had difficulty in keeping food from falling into the windpipe or passing into the nose. Six years before, she had noticed gradual wasting and weakening of the right shoulder and arm which had continued to ache since the onset of the trouble. The tonsils and many teeth had been removed without relief. She had had headache over the right occipital region often. The right side of her tongue had felt thick and at times she had difficulty in speaking.

Examination of the right side of the tongue revealed paralysis and atrophy. The right side of the palate, pharynx, and larynx was paralyzed, and the right trapezius and sternocleidomastoid muscles were atrophied. The right vocal cord was in the intermediate position. There was a collection of food in the right hypopharynx. Roentgen-ray examinations of the head and of the cervical spine were negative; examination of the eyes and the Wassermann reaction on the blood were negative.

Summary. This case illustrates involvement of the ninth, tenth, eleventh, and twelfth cranial nerves on the right side, probably owing to a mixed tumor in the region of the jugular foramen.

Discussion. In 6 of the 7 cases in the series there was unilateral complete laryngeal paralysis associated with the jugular foramen syndrome or other syndromes, and in 1 case (Case VI), there was paralysis of the right side of the palate and pharynx, and involvement of the second, third, fourth, fifth, sixth, eleventh, and twelfth cranial nerves and of the cervical sympathetic nerve, without laryngeal paralysis. In all the cases in which the larynx was paralyzed the vocal cord was in the intermediate or cadaveric position and not in the middle position usually taken by it after an injury to the recurrent laryngeal nerve.

Cases II and VI are unusual on account of the extent of the involvement of the nerves. In Case II the third, fourth, and sixth nerves were probably affected in the orbit owing to extension of the epithelioma. The fifth and seventh nerves were probably affected intracranially, and the ninth, tenth, eleventh, and twelfth nerves by direct extension of the tumor to the region of the jugular foramen. The patient was deaf on the side involved because of encroachment on the Eustachian tube in the nasopharynx. In

Case VI a nasopharyngeal tumor affected the second, third, fourth, fifth and sixth nerves, probably intracranially, and the ninth, tenth, eleventh and twelfth, and the cervical sympathetic nerves in the region of the jugular foramen.

The cervical sympathetic nerve was affected in 4 cases as shown by myosis and narrowing of the palpebral fissure.

In a review of the entire group several points of interest may be noted. In all of the cases, except possibly Case I, involvement of the nerves was due to neoplasm in the region of the jugular foramen, and even in this case such involvement is the most probable cause, although it is possible the medulla was affected.

In 6 cases the nerve involvement was caused by a tumor. In 4 of these cases the tumor was slow-growing and of a low grade of malignancy; the duration of symptoms ranged from two to twelve years. One lesion of the series was microscopically proved to be carcinoma of the mixed-tumor type. Two growths were clinically mixed tumors and 1 a recurring basal-cell epithelioma. In 2 of the 6 cases the pathological lesion was a rapidly growing tumor, probably a lymphosarcoma, the symptoms of which were present from three to six months only. In these cases the tumor originated in the nasopharynx and pharynx.

The age of the patients was from thirty-five to sixty-two years and the duration of the symptoms from six to twelve years. The males and females were about equally affected.

Definite cardiac or respiratory disorders did not occur, except in Cases I and V. The patient in Case I complained of palpitation and dyspnea on exertion; but she had been operated on for toxic goiter. In Case V the patient complained of pounding of the heart and dyspnea when climbing stairs. Examination of the heart showed loud systolic murmurs at the apex, transmitted to the axilla.

In examining the patients it was noted that those with paralysis of half of the tongue had trouble in swallowing liquids, an act effected by means of pressing the tongue against the hard palate. Paralysis of the palate caused food to become lodged back of the nose. Paralysis of the muscles of the pharynx interfered with the swallowing of solids.

In some of the 7 cases in the series it was difficult to determine definitely the degree of involvement of the ninth and tenth nerves, but this is because of our vague understanding of the anatomy and physiology of this region.

Summary. It may be seen from a review of the cases in the literature and of my group of cases that laryngeal paralysis associated with a syndrome due to involvement of the last four cranial nerves and the cervical sympathetic nerve in the region of the jugular foramen is quite unusual. When this occurs it is usually

owing to a neoplasm, although a tuberculous process in the glands of the neck or an acute phlegmon may be the cause. During the World War cases were reported due to bullet or shrapnel wounds. The vocal cord is in the intermediate or cadaveric position in vagus involvement.

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THE PATHOLOGY OF NODULAR (ADENOMATOUS?) GOITERS IN PATIENTS WITH AND IN THOSE WITHOUT SYMPTOMS OF HYPERTHYROIDISM.*

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The pathologic changes met with in the thyroid in true exophthalmic goiter are now well agreed on. Briefly, the disease as indicated in the changes in the thyroid may be divided into three general stages:

1. Early exophthalmic goiter, with moderate increase in basal metabolism and usually moderate exophthalmos. In this condition there is moderate thyroid enlargement. The parenchymal cells show marked hypertrophy and moderate hyperplasia. There is diffuse hyperemia throughout the gland.

2. Advanced exophthalmic goiter with high metabolic rate, usually marked exophthalmos and a well-marked nervous syndrome. There is usually marked thyroid enlargement. There is advanced parenchymal cell hypertrophy and hyperplasia. There is little if any stored colloid. There is diffuse hyperemia throughout the gland.

3. Late exophthalmic goiter with high but sometimes declining metabolic rate, exophthalmos and a well-marked nervous syndrome. Pathologically the changes in the gland are similar to those in the earlier stages of exophthalmic goiter but with beginning or well-marked storage of colloid. Many follicles containing colloid are lined with flattened parenchymal cells. In some instances newly developed follicles are numerous. Hyperemia is usually materially less than in glands in the previous groups.

The parenchymal changes in the thyroid in true exophthalmic goiter are almost always diffuse and, therefore, the gland is rarely nodular in its gross appearance.

As pointed out by H. S. Plummer, related to, but clinically distinct from, exophthalmic goiter is a large group of patients with symptoms usually of slow development or, if rapidly developing, only after a long period of non-symptomatic thyroid enlargement, with basal metabolism increased as much as in exophthalmic goiter but usually with no ocular symptoms, and without the nervous syndrome peculiar to exophthalmic goiter. This type of hyperthyroidism is so often associated with nodular thyroids that Plummer tentatively designated the disease first "toxic non-hyperplastic goiter," then "toxic adenoma" and now "hyperfunctioning adenoma."

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Before the routine determination of basal metabolic rates was established in the Mayo Clinic it was difficult to select groups of patients representing on the one hand well-marked stages of this syndrome and on the other, patients entirely free from the symptoms. Since 1908, I have made several attempts at a comparison of specimens from groups of such cases selected on a clinical basis only, but previously I have never been able to determine any marked general difference between groups of thyroids from the two types of cases. This was due in part to the necessary shifting of the group as it was being clinically differentiated, and in part to the failure first to compare thyroids from patients with extreme symptoms with those from patients without symptoms. During the last year, however, I have been able to study two groups at the extremes of the metabolic series selected in chronologic order of occurrence by Dr. Boothby.

Group A. Patients with enlarged nodular thyroids, with symptoms of hyperthyroidism but without exophthalmos, without the nervous syndrome peculiar to exophthalmic goiter, and with basal metabolic rates of 20 or more points above normal.

Group B. Patients of approximately the same age with enlarged nodular thyroids, without symptoms of hyperthyroidism and with basal metabolic rates within 10 points of normal.

I have studied the thyroids from about 250 patients in each series, or a total of over 500 thyroids.

The specimens were all placed in 10 per cent formalin within a few minutes after their removal and, after complete fixation, sectioned by freezing and stained with hematoxylin and eosin. Some of them were also imbedded in paraffin and the sections stained by other methods. Every effort was made to adhere to parallel processes throughout the technic of preparing the sections. The cases were numbered chronologically and the two series placed in separate trays beside each other for convenience in comparison. This work was done for me by Dr. C. W. Barrier, of the Mayo Foundation, in the course of a piece of research on the thyroid he was carrying on for himself.

The examination of the first twenty specimens, that is, ten from each series, showed such a marked difference between the two series that I immediately took the specimens numbered 51 to 60, 101 to 110, 151 to 160, 201 to 210, and so forth from each series and carefully compared them. The results in these widely separated decimal groups were so parallel with those in the first ten that I was satisfied no error of technic could explain the findings. I therefore went back and studied more leisurely all the specimens in each series, comparing each number not only with the corresponding number in the other series but also with many others. The results of this examination are as follows:

1. About 90 per cent of all thyroids in Group A show in one or

more of the areas from which sections were examined distinct evidence of increased activity of the parenchymal cells. This is indicated by moderate degrees of cell hypertrophy and hyperplasia associated usually with some colloid storage. In many there are areas in which the follicles are closely packed with dense colloid, but there are also many areas showing follicles containing little or no colloid, and lined with hypertrophic parenchymal cells. Where colloid is present it has a distinctly lighter staining reaction than that in thyroids in Group B. In many instances there is considerable parenchymal cell hyperplasia.

Grossly many of the glands are (*a*) diffuse colloid goiters without any evidence of new follicle formation, but whose nodular character is the result of increased and contracting interlobular connective tissue usually associated with round-cell infiltration indicating chronic inflammation; or (*b*) colloid goiters with definite new follicle formation but without definite capsule formation, (adenomatosis) with many of the new follicles lined with parenchymal cells of functioning type which are hypertrophic, or (*c*) definitely encapsulated areas of new follicle formation (adenomas) with hypertrophic and often hyperplastic parenchymal cells lining follicles which contain little or no stored colloid. All of these hypertrophic and hyperplastic changes are so moderate in degree and in amount as readily to escape notice except by careful comparison of a large number of thyroids from patients with high metabolic rates side by side with a like number of thryoids from patients exhibiting no increase in basal metabolic rate.

In comparing the changes in the thyroids in Group A with the changes in the thyroids in a series of typical exophthalmic goiter cases it is found that in general the difference is not only one of degree but in most instances also of kind. The most advanced parenchymal cell hypertrophy and hyperplasia found in any case in Group A, is about the equal of the more moderate degrees of parenchymal cell hypertrophy and hyperplasia in thyroids from the true exophthalmic goiter series; but in most of the thyroids in Group A the histologic picture shows that there has been marked colloid storage in most of the follicles and that now the stored colloid is apparently being taken up by the parenchymal cells and passed into the circulation. The parenchymal cells are apparently not, under high functional pressure, discharging their secretion directly into the vessels as is the case in exophthalmic goiter, but are first storing it in the follicles. A very common picture in these specimens is the presence in one portion of a large follicle, most of which is filled with dense stored colloid, of small areas of very lightly staining colloid in immediate opposition to hypertrophic or hyperplastic parenchymal cells, while the parenchymal cells lining other portions of the follicle are flattened and atrophic. The chief departure from this picture in thyroids in Group A is

in those instances in which there is very marked formation of new follicles. These, in definitely encapsulated "adenomas," may contain dense stored colloid. Where there is diffuse new follicle formation without definite encapsulation the follicles are not likely to contain colloid, or if any, it is feebly staining. The number of the former type of glands is, however, much greater than of the latter. From the pathologic evidence alone we are not warranted in concluding that the formation of new follicles is the essential factor in the production of hyperthyroid symptoms, since in almost all glands, even in which this is the predominating picture, there are to be found as well many areas which indicate absorption of colloid by reactivated parenchymal cells.

About 95 per cent of the thyroids in Group B, that is from patients with nodular goiters with the clinical diagnosis of adenoma without increased basal metabolic rates or other symptoms of hyperthyroidism, showed in none of the sections from any of the areas examined evidence of even moderate degrees of cell hypertrophy and hyperplasia. The parenchymal cells in follicles of adult type were uniformly flattened or atrophic. In most follicles in adenomas they were of very undeveloped embryonic type. The intra-follicular colloid stained much more densely than that in thyroids in Group A. Grossly the thyroids from these patients could readily be divided for the most part into three groups closely paralleling those of glands from the hyperthyroid series. A few of the specimens consisted of proliferating adenomas, Langhans wuchernde Struma. It should be noted that the patients from whom these thyroids were removed had been grouped clinically on the basis of nodular goiters. Had the marked nodular character of the thyroids not been recognized clinically no doubt some thyroids would have been found in which the colloid was evenly distributed throughout all the follicles which were lined with flattened or atrophic parenchymal cells, and their interlobular bands of connective tissue would not have been found to be abnormally increased or contracted.

Owing to the work of Boothby and others we may now safely assume that in thyroid disturbances the basal metabolic rate is a true index of the degree of hypothyroidism and hyperthyroidism. It follows then that the high incidence of moderate parenchymatous cell hypertrophy and hyperplasia in thyroids from the patients in Group A and its absence from almost all thyroids of patients in Group B can be rationally explained on the basis of a causative relationship. That is, the hypertrophic and hyperplastic parenchymal cells in Group A are apparently secreting a substance which is probably responsible for the symptoms and the increased metabolic rate, and on the other hand no substance in sufficiently large amounts to excite symptoms or increase the metabolic rate apparently is being secreted by the parenchymal cells in the follicles

of the thyroids of Group B. No doubt some of the instances of non-conformity in Group A and also those in Group B may be explained by technical errors, for example: Failure thoroughly to search sufficiently numerous areas in the glands for evidence of increased cell activity. It would seem reasonable to assume, however, that the finding of moderate degrees of cell hypertrophy and hyperplasia in about 5 per cent of the thyroids in Group B may be explained by the supposition that not enough increase in cell activity had occurred to induce symptoms of hyperthyroidism or to increase the metabolic rate.

It is a very inviting hypothesis that the symptoms of non-exophthalmic hyperthyroidism are caused by the adsorption of complete thyroxin in previously stored colloid which is being manufactured more rapidly than in the normal gland but much more slowly than in the thyroid of exophthalmic goiter. This hypothesis receives support from the facts that the symptoms produced by the administration of thyroxin in large doses to human beings are essentially those of non-exophthalmic hyperthyroidism, that stored colloid does contain thyroxin and that the histologic picture indicates that colloid is being transferred from the follicles to the circulation.

On the other hand we might go a step further and speculate on the probability that true exophthalmic goiter is caused by an incompletely elaborated thyroid secretion, an antecedent of thyroxin but not with its normal quota of its atoms of iodine in the molecule, for example. Such a hypothesis would harmonize many of the clinical and pathologic findings. However, an equally alluring hypothesis is that in true exophthalmic goiter the primary onset of the disease is in the nervous system and that the more significant thyroid hyperfunction is nevertheless a secondary development.

THE CLINICAL CRITERIA OF ACTIVITY IN PULMONARY TUBERCULOSIS.*

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Every physician having to do with the diagnosis and treatment of pulmonary tuberculosis is asked by his patients whether they have *any* activity, *more* activity, or *less* activity. To these questions an answer must be given, as in that answer is contained that which is most important to the patient, his improvement or the

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reverse. Conflicting statements are not infrequently made to patients by competent examiners at periods so close one to another that a change in pulmonary conditions is out of the question. There is evidently a difference in the conception of activity on the part of many well qualified men, and there is also evidently a lack of standardization with regard to what actually constitutes the existence of activity.

First of all activity must be defined. This is not so easy. "Infection greater than resistance." "Evidence of poisoning, local and general, by the toxins of the tubercle bacillus." "Onward progress of the tuberculous process." "The picture presented and the physical signs elicited as a result of intoxication with the poisons of the bacillus of tuberculosis." "Tuberculous disease as opposed to tuberculous infection." These are a few of the definitions that present themselves.

There are, broadly speaking, five bases for the estimation of the presence of activity. These are:

1. Palpatory.
2. Radiological.
3. Auscultatory.
   - Rales.
     - Dry.
     - Moist.
4. Laboratory methods.
   - Bacilli in sputum.
   - Arneth's differential leukocyte count.
   - Complement-fixation.
5. Symptomatic.

1. *Palpatory.* The palpatory estimation of activity has found but little favor at the hands of the profession as a whole, though its few adherents are enthusiastic as to its value. Pottenger who has lauded it most highly, claims that by the rigidity of the muscles overlying the lungs which can be appreciated by the palpating fingers, the site of the lesion can be accurately determined, and moreover, that by the intensity of this rigidity the grade of activity can be estimated. Such a highly developed palpatory sense is vouchsafed to few, and just as to the man doing but little lung work, percussion is not as a rule of much aid, so to the majority of workers in tuberculosis the palpatory determination of activity has remained a sealed book.

2. *Radiological.* In the past decade the routine use of stereoopic roentgen-ray plates in chest diagnosis and study has opened a tremendous field for good and also for confusion. There is at present between the radiologist and the clinician much dispute as to the true significance of the picture. The radiologist with his greater mechanical and technical knowledge, often avers that he has discovered evidences of pulmonary activity where the clinician,

fortified by his general knowledge of the patient and by his physical examination, feels that such activity does not exist. Many patients have been declared actively tuberculous by the radiologist in whom the subsequent evolution of their condition showed them to be at most subjects of tuberculous infection and not victims of tuberculous disease. The roentgen-ray as the sole evidence of tuberculous activity should not be relied upon. As an adjuvant, and as a corroborator of other pathological evidences or of merely suggestive symptoms, it is in the very forefront of diagnostic aids. The roentgen-rays will almost invariably shame the examiners' fingers and ears, but comfort can be derived from the fact that the plate may be said to present a pathological picture, while the other methods of physical examination may be said to present a clinical picture. How often in the absence of any detectable change in the breath sounds and in the absence of any adventitious sounds will the plate show not alone peribronchial thickening but also cotton-ball shadows of various sizes! These latter we know usually betoken the coalescence of tubercles with consequent softening, and indicate active disease. If other evidences of activity are at hand, we must unquestionably accept these radiological signs as evidences of active trouble; if, on the other hand, all other evidences are wanting, we must be cautious in discarding these shadows as unimportant, and while perhaps not coming out openly and saying that no activity exists, we must keep the patient under careful supervision for many weeks until certainty of judgment can be reached.

3. *Auscultatory.* The appreciation of the presence of activity by auscultation is the method of examination at present most relied upon, and that which, in the long run, will be of the greatest service to the greatest number of physicians. Valuable it is indeed, and yet the interpretation of the auscultatory signs is so varied that differences of opinion are often forthcoming even between men widely recognized as experts. Estimation of activity by auscultation should be restricted to the presence, location and character of rales, and should not be concerned with the breath sounds. Rales are in themselves a great stumbling block. Much depends upon their location and their character, it being really superfluous to repeat that basal rales are of infinitely less importance than apical rales. This observation would indeed not have been made had it not been for an experience of the writer while in the service, when requested by the head of the tuberculosis board at one of the camps to go over six men that had been slated for an S. C. D. (Surgeon's Certificate of Disability), to find the only abnormality to be a few fine marginal rales at both pulmonary bases. These signs and these alone were the evidence upon which discharge from the service had been deemed wise. The moist rale has ever been the one that is held to betoken activity. It matters not whether it be a fine or a coarse moist rale. Well and good as far as it goes, but it is by no means always easy even for men of large experience to distinguish

between a moist and a dry rale. To be sure, extremes of either variety can easily be recognized, but in the appreciation of the borderline sounds the personal equation plays such a part that an absolute standard is not obtainable. None the less, it is an indisputable fact that moist rales, not sibilations or large ronchi, but true moist rales, denote an active process. The pleuritic friction, when accompanied by other evidences of illness, is also a physical sign of paramount importance.

4. *Laboratory Methods.* Tubercle bacilli in the sputum, while diagnostically the one positive proof of pulmonary tuberculosis, have been held by some to be an evidence of activity. This has never impressed the writer as being a tenable position. Tubercle bacilli in the sputum merely indicate the presence of an ulcerated tuberculous process in the lung, through which the bacilli are enabled to reach the bronchial tree. To be sure, if 100 patients with positive sputum be compared with 100 patients with negative sputum, the majority of actively ill individuals will be found in the positive group; but all men doing lung work see not infrequently patients with a quiescent lesion doing a full day's work right along, and having a teaspoonful of sputum per day, even per week, in which tubercle bacilli are constantly to be found. If such individuals are to be classed as "active" cases, they have at any rate achieved an "economic recovery" which is the great goal of all the tuberculous, and the question of "activity" becomes one of merely academic interest.

The Arneth differential leukocytic count, simple to make, has had numerous followers. The count is a differential one of the polymorphonuclear neutrophiles based upon the number of nuclear lobes that they possess, namely whether 1, 2, 3, 4, or 5. Arneth claims that in active cases the preponderance of the cells are found to have one or two lobes, whereas in inactive or negative cases the majority have three, four or five lobes. Thus in active cases there results a "shift to the left" (Verschiebung nach links) of the dominating percentages, classes 1 and 2 being naturally to the left of the percentage table as it is recorded on the paper. Several years ago my associate, Dr. C. L. Minor,[1] and myself[2] did fairly extensive work with this method, studying some 475 cases with a total of almost 800 counts. An initial enthusiasm for the method gradually waned with increasing experience, and a final conclusion was reached that, while generally corroborative, the method was too unreliable to secure for itself a place among the true criteria of activity.

The complement-fixation test, while it has had some supporters, is not to be compared in reliability to its kinsman the Wassermann

[1] Arneth's Method of Blood Counting—Its Prognostic Value in Pulmonary Tuberculosis, Am. Jour. Med. Sci., 1911, **141**, 638.

[2] Ringer, P. H.: A Further Study of the Prognostic Value of Arneth's Leukocytic Blood Picture in Pulmonary Tuberculosis Based upon 729 Counts in 475 Patients, Am. Jour. Med. Sci., 1912, **144**, 561.

reaction, and has hardly stood the acid test as a criterion of activity in tuberculosis.

5. *Symptomatic.* The realm of symptomatology, in the writer's opinion, is that furnishing the most valuable evidences of tuberculous activity. In our routine and periodic examination of patients, while all possible care is taken to keep track of both extent and character of adventitious sounds and of variations in the stereoscopic picture, the opinion given to the patient as to improvement or the reverse (in other words as to lessened or increased activity), is based mainly upon the contents of the column labelled "Symptoms" on the examination chart. A patient whose temperature is lessening, whose pulse is slowing, whose appetite and sleep are growing better, whose weight is going up, must be and is improving even though cough and sputum may be practically unaffected and physical signs stationary. It is rare to find marked lessening of cough and especially of sputum in the absence of some change for the better in the physical signs, but even if this change is not demonstrable, a betterment in symptoms justifies a frank expression of opinion to the effect that activity is on the wane. Changes in physical signs are not of such prime importance as they were once conceived to be. As an example of this may be quoted the interesting statistical study made by Dr. Francis B. Trudeau[3] of a total of 979 cases discharged from the Trudeau Sanatorium with special reference to the physical signs.

RESULTS OF 979 CASES AT TRUDEAU SANATORIUM.

	No.	Per cent.	Per cent well.	Per cent living.	Per cent dead	Per cent unknown.
Increase in physical signs	422	43.1	52.9	14.7	31.0	1.4
Decrease in physical signs	398	40.6	69.8	12.8	15.8	1.5
No change in physical signs	159	16.3	78.0	10.7	10.1	1.2

This study shows of course that in general an increase in signs is of bad import and signifies progressive activity, which is really self-evident, but it also shows that it matters much less whether the physical signs decrease or remain stationary. As a matter of fact, Dr. Trudeau's figures for the "well" class in those showing "No Change" are better than in those showing "Decrease" in signs (78 per cent as against 69 per cent), though this is probably accounted for by the far greater number (398 as against 159) that were included in the "Signs Decreased" table. I would not be thought to wish to give little or no importance to extent of, character of, and changes in physical signs, but I do wish to stress the point that in the estimation of pulmonary activity symptoms have vastly greater weight. Moreover, symptoms are tangible, palpable facts in which the personal equation of the physician, the acuity of his hearing, the technic of his roentgen ray or of his laboratory play

[3] The Importance of Physical Signs in the Prognosis of Pulmonary Tuberculosis, Trans. Nat. Tuberc. Assn., 1920, p. 283.

no part. Variations in weight, range of temperature, fluctuations of pulse, measurement of daily sputum, amount of food consumed, hours of sleep, improvement in hemoglobin and red cells, general increase in vitality and good feelings on the part of the patient, all these save the last can be determined by instruments of precision requiring no special training for their use, and nothing beyond ordinary common sense for their correct interpretation. It is on these data that a correct basis for the estimation of activity of tuberculous disease can best be established.

I will not bore you by citing examples illustrative of all the points I have made, but will limit myself to reporting three widely differing cases, each of which stresses a certain phase of the subject.

The first of these shows the danger in relying solely upon a radiological diagnosis of tuberculous activity when symptomatic corroboration is lacking. This patient consulted her family physician, who made no examination but referred her to a very prominent radiologist, who took and interpreted the plates and sent in a report of peribronchial thickening suggestive of active tuberculosis. On the basis of this report alone she was adjudged actively tuberculous and sent to us.

Case I.—Mrs. X., aged thirty-six years. Paternal grandfather and grandmother and one uncle died of tuberculosis. One brother now in the West because of tuberculosis. Childhood history negative. Was never exposed to any of the tuberculous members of her family. Married at twenty-one, has one child, aged eight years. Never well since the birth of this child when she had a very difficult labor. Suffered a third degree perineal tear which was repaired at the time, but not satisfactorily. Four years later a trachelorrhaphy and perineorrhaphy were done. For a while she felt better, but then began to flow profusely for eight days every three weeks. Finally a hysterectomy was done in June, 1919, the ovaries and tubes being left. (I am not sure whether both ovaries were left or only one). There was no particular improvement in her feelings after this operation. For the past year has lost all energy and enthusiasm. Has taken every kind of tonic but to no avail. Is exceedingly nervous, crying frequently. For the past few months has run some temperature, between 99 and 100°F., the latter rarely. Teeth have been pronounced sound after being radiographed twice. *At no time has there ever been any cough or sputum.* Spirits very poor. Nutrition bad; sleeps poorly; perspires very freely; appetite poor; bowels constipated. Physical examination of the lungs was absolutely negative. Stereograms showed some peribronchial thickening but not enough in our opinion to warrant a diagnosis of active tuberculous disease in view of the history and symptoms. The patient was told she did not have any active tuberculosis, and a diagnosis of psychasthenia with possibly some endocrine disturbance was made. She was placed in a neurological sanatorium on a rest cure for a

period of three weeks and received as medication ovarian extract and thyroid extract. In addition she was given psychotherapy, in the course of which a domestic infelicity was brought to the surface and largely cleared up. In four months she had completely recovered. All symptoms had disappeared and she returned home happier and better than she had been in years. This condition of health had persisted for over two years when she was last heard from at Christmas, 1921. The history in this case, mainly nervous and gynecological, the long duration of asthenia, the absence of any focal symptoms or signs of tuberculosis, did not warrant a diagnosis of activity on the peribronchial thickening demonstrable in the stereograms. In addition to her endocrine disturbance and functional nervous disorder, this woman had a tuberculous infection, to which she was entitled, being thirty-six years of age, but she did not have tuberculous disease.

The second case illustrates the diagnosis of tuberculous activity on symptoms in the complete absence of physical signs, but with definitely positive stereograms.

CASE II.—Mr. Y., aged twenty-six years. Family and childhood history negative. In U. S. Army, 1917–1919; overseas eighteen months, slightly gassed. Average weight, 150. Has dropped to 132. Discharged from the service in 1919 as physically fit. Has not felt perfectly well since his discharge. Tires very easily and has frequent and repeated colds with cough and sputum. There has been some blood in the sputum at times, but never any frank hemoptysis. In September, 1921, had bronchopneumonia and was ill three weeks. Has not been able to work since with any regularity, owing to rapidly appearing fatigue. Now there is slight cough, slight sputum, which is constantly negative for tubercle bacilli, temperature ranging at its maximum from 99.2 to 99.6, daily, very little endurance and dyspnea on slight exertion. Physical examination of the lungs, both at my hands and at those of Dr. Minor was absolutely negative, but the stereograms showed very distinctly a lesion at the right apex, appearing as a group of ten or twelve cotton-ball-like masses. A diagnosis of active tuberculosis would, in my opinion, have been justifiable on the symptoms alone, though I confess it was a comfort to find that our surmise was borne out radiologically.

It is interesting to note that during the three months that have elapsed since this diagnosis was made, a few fine rales have made their appearance first opposite the spine of the right scapula, and later in the first intercostal space on the same side, so that now this patient presents both symptoms, radiological evidences, and physical signs.

The third case illustrates marked improvement in general condition with consequent lessening of activity, according to the premise

of this paper, and yet with no change to speak of in the physical signs at the end of seven months.

CASE III.—Mrs. Z., aged forty-one years, came to us September 9, 1921. It is unnecessary to go into the details of her history. She had a definite advanced right-sided pulmonary tuberculosis without complications. On arrival her weight was 96 (average weight in health, 125; best weight, 130; standard insurance weight, 135). She had considerable cough and a little over one ounce of sputum. Temperature ranged from 99 to 100°F. She was weak and dyspneic. Her pulse was not unduly accelerated. On physical examination, she showed dulness on the right side to the third rib in front and to the fifth vertebral spine behind. Auscultation revealed broncho-vesicular breathing over a similar area with feeble breathing over the rest of the lung. Fine moist and dry rales were to be heard over the entire front of the right lung, and over the back to about an inch above the angle of the scapula. There were tubercle bacilli in the sputum. Her present condition is: Weight, 128¼, a gain of 32¼ pounds; temperature absolutely normal; cough very slight; sputum about half an ounce in twenty-four hours; no dyspnea; strength so much improved that she can walk from forty-five minutes to one hour at a stretch without becoming fatigued. Physical and radiological examination, however, reveal conditions to all intents and purposes identical with those found in September as regards dulness, broncho-vesicular breathing, extent and quality of rales, and roentgen-ray shadows. This patient is, nevertheless, a totally different woman from what she was seven months ago; her friends would not recognize her—she has improved wonderfully. Her symptoms are all better, and many of them have disappeared entirely. Unquestionably we must assume that activity has greatly lessened and this assumption is based not on changes in physical signs or radiological findings, but on changes in symptoms the intensity of which are the main criteria for estimating the potency of the general infection.

Summary. Thus we see that the more we study the various forms of pulmonary tuberculosis, the more we are driven to symptoms in our estimation of the presence or absence of activity. Refinements of physical diagnosis lie in the province of the pulmonary expert; refinement in plate reading in that of the radiologist; refinements in laboratory methods in that of the clinical pathologist; they are all useful, and each one of us should master all of them that he can; but for the man doing general work, the estimation of the presence or absence of activity in tuberculosis will be based in the main upon the careful consideration of symptoms which alone point out the relative strength of the two great fundamental biological factors in any infectious disease; virulence of the invading parasite, and resisting powers of the invaded host.

REVIEWS.

MINOR SURGERY AND BANDAGING. By HENRY R. WHARTON, M.D., Consulting Surgeon to the Presbyterian Hospital. Ninth edition. Pp. 647; 450 illustrations. Philadelphia: Lea & Febiger, 1922.

THIS edition is a distinct improvement over the last. The book is well arranged, the reading matter easy and the style clear and concise. Illustrations are excellent and profuse. The table of contents and index are so arranged as to make the subject-matter easily accessible with a minimum of effort. The parts dealing with bandaging, asepsis and antisepsis, fractures and dislocations are full and well handled, giving the optimum of instruction with the minimum of verbal effort. Ligation of arteries and minor operations are treated under separate chapters. The subjects of anesthesia and transfusion are covered in great detail, but certain parts dealing with a number of minor surgical affections are a trifle brief.

This work has made and should continue to make an excellent and handy text-book for the general practitioner.

H.

DISEASES OF THE NERVOUS SYSTEM. By SMITH ELY JELLIFFE, M.D., PH.D., formerly Professor of Psychiatry, Fordham University, and WILLIAM A. WHITE, M.D., Professor of Nervous and Mental Diseases, Georgetown University. Fourth edition, revised, rewritten and enlarged. Pp. 1119; 475 engravings and 13 plates. Philadelphia: Lea & Febiger, 1923.

THIS new edition of such a well-known book does not require a great deal of comment. The authors have kept in view the idea of producing a work which is not merely a collection and arrangement of a mass of facts, but one which will stimulate the thought of the student using it conscientiously. And in this they have succeeded most admirably. Doubtless, neurologists may differ in regard to some of the opinions expressed by the authors, but no one of them can deny the thought-stimulating power of the book.

The high standard reached in the earlier editions has been made still higher in this one, not only by the new matter which has been added and the parts which have been rewritten, but more especially by the character of the work in general and the method of treatment of the subject as a whole.

A prominent feature of the book is the number of excellent figures and charts which help to a much clearer understanding and more exact diagnosis of the various conditions considered. M.

AN INTRODUCTION TO THE PRACTICE OF PREVENTIVE MEDICINE. By J. G. FITZGERALD, M.D., F.R.C.S., Professor of Hygiene and Preventive Medicine and Director of Connaught Laboratories, University of Toronto; assisted by P. GILLESPIE, M. Sc., and H. M. LANCASTER, B.A.Sc. Pp. 826; 129 illustrations. St. Louis: C. V. Mosby Company, 1922.

As the title of this book indicates, it does not pretend to be a complete exposition of the whole field of preventive medicine in all its details, but is merely an introduction to the practice of that branch of medicine. The idea in the mind of the writer would seem to have been to produce a book which would not frighten the general practitioner by its bulk, but which would rather stimulate his interest in the subject and help him to realize the importance of the part he should play in the campaign for the prevention of disease.

If viewed in this light, the book takes on a different character from that which otherwise might be given to it, and the value of having the various questions presented in a fairly brief, but very clear manner, is at once perceived. The author has received the assistance of certain authorities in writing special sections, such as those relating to water, milk, diet, sanitation, etc., so that one appreciates that the book presents the most recent ideas in preventive medicine. M.

TWELVE ESSAYS ON SEX AND PSYCHOANALYSIS. By WILHELM STEKEL, M.D., Vienna: translated and edited by S. A. TANNENBAUM, M.D., New York. Pp. 320. New York: The Critic & Guide Company, 1922.

THESE essays cover a period of ten years, most of them having appeared in print between 1909 and the beginning of the War. In the theses presented by the author, there is plenty to offend some, who, through ignorance or conviction, are opposed to the doctrines of psychoanalysis. Among those more sympathetic,

some do not agree in detail with all the conclusions of the author, for highly controversial matter is involved. The style is vivid, but perhaps not so conspicuously epigrammatic as some later works of the same author. These studies contain much sound truth and much that challenges the psychiatrist's attention; they should not be overlooked by any physician who deals with neurotics, exhibitionists, thieves or suicides, especially if he is concerned to protect the young from joining any such group. What is said of onanism is to be heeded in quarters whence comes much sincere but badly devised propaganda on sexual themes.

The essay on "Sexual Abstinence and Health" has been widely quoted since its publication in 1909. The author sets forth characteristics of the "supposedly innocent child," the power of instinct and the demand for sexual activity. He presents a situation involving practical difficulties for the conscientious physician of this land, though perhaps the difficulties are less under Continental culture. He would punish one who knowingly infects another, and legalize abortion before the fourth month. He would enlighten children gradually and postpone gross sexual stimuli as long as possible. Onanism is discussed, its implications, frequency and comparative harmlessness. His views on sleep and insomnia differ in some points from those traditional; for instance he asserts that sleep does not strengthen the nerves. Happy persons, he says, never complain of insomnia. Homosexuality is presented as frequent but tremendously repressed. Suicide is not considered a logical or philosophical act, but one determined fundamentally by a sense of guilt. It was growing more frequent among children when this essay was written, and particularly among the children reared in small families. Obsessions are presented as results of the repression of an unacceptable idea. The obsessed neurotic's character is discussed. Exhibitionism is next considered and its relation to the neurotic character and to onanism. The dramatic instinct of the neurotic and his piety and belief in his mission are described, together with notes on treatment. The neurotic's obscuration of the border between fantasy and reality, the annulment of reality and his attitude toward time are ingeniously presented. The book ends with a discussion of the psychology of kleptomania, relating it to early sexual stimulation and the temptation to do something forbidden. The translator has interlarded many comments of his own, bracketing them from the rest of the text. These comments amplify the subject and rarely suggest a different view or a feeling that the original statement needs defense. If one must add to a text this is perhaps the best way, through brackets sometimes offend the eye of the reader.

Fortunately we are now in a period when psychoanalysis is discussed with less bitterness than used to be aroused. The author has done important work in this field and his formulations are still important. H.

CHARLES WHITE OF MANCHESTER (1728–1813), AND THE ARREST OF PUERPERAL FEVER (the Lloyd-Roberts Lecture, Manchester Royal Infirmary, 1921). By J. GEORGE ADAMI, C.B.E., M.D., F.R.S., Vice-Chancellor of the University of Liverpool. With which are reprinted Charles White's published writings upon puerperal fever. Pp. 142; 4 illustrations. Liverpool: The University Press, Ltd.; London: Hodder & Stoughton, Ltd., 1922.

THIS scholarly lecture is a most delightful historical sketch of that famous British surgeon, obstetrician and hygienist, Charles White, whose far-sighted teaching and keen analysis of the cause of puerperal fever clearly establishes a prior claim for him in the matter of prophylaxis and prevention of that malady.

To the lecture are appended chapters from the writings of Charles White. Would that every parturient today might be delivered under the safe, sane and sensible directions he laid down in the year 1773. Then one of the scourges of child-bearing would be minimized. This book will be of interest to all medical historians and obstetricians. W.

SOME MEDICAL ASPECTS OF OLD AGE. By SIR HUMPHRY ROLLESTON, K.C.B., M.D., D.C.L., LL.D. Being the Linacre Lecture 1922, St. John's College, Cambridge. London: The Macmillan Company, 1922.

IN this "*De Senectute*," Sir Humphry Rolleston has skilfully combined a discussion of some of the general features of old age with considerations more strictly medical. It is a subject in which we all will be interested if we live long enough. The basis of the book is the material collected for the Linacre Lecture at St. John's College, Cambridge, of which Sir Humphry was at one time a Fellow.

The duration of life in higher and lower forms is discussed in a general way and there are portraits of several traditional "oldsters" who are reputed to have lived beyond the usual time, including Henry Jenkins with one hundred and sixty-nine years and a Hungarian with one hundred and eighty-seven years. The author is sceptical as to the correctness of certain of these records. He gives explanations but does not decide the question as to the duration of the life of Methuselah.

When does old age begin? The author points out that it is often unrecognized by the victim himself until perhaps some chance remark or occurrence brings it home to him. The influence of heredity, environment and past diseases on longevity are considered and the evil effect of syphilis is emphasized. Much stress is placed on functional activity and the evil of autosuggestion is mentioned:

"I am getting older and older every day" has its harmful influence. The often injurious effect on a healthy old man of giving up work is pointed out. This is a subject on which our advice is not infrequently asked and the decision is often difficult. Perhaps of chief importance is whether or not there is an *avocation* to which he can turn when the *vocation* is given up. The wise man cultivates a hobby in his maturity. Some have held that the attainment of old age is in great part a matter of the will. As Strachey says of one circle, "They refused to grow old; they almost refused to die." As to personal habits, the observation that the majority of those who have reached old age are small eaters of meat is noticed and the use of alcohol even in moderation is regarded as unfavorable. Among the causes of senescence the influence of the endocrine glands is discussed. The conclusion is reached that changes in the interstitial cells are not the cause but an accompaniment of old age. As to the use of thyroid and other gland extracts a word of caution is given, for harm may be done by stimulating metabolism overmuch. The discussion of the normal structural changes and physiology of old age dwells more on the purely medical aspects. The attitude toward death is described as rarely showing a desire for rest, as one might long for sleep, but rather there is "a passionate, absorbing, almost bloodthirsty clinging to life."

This is a delightful little book, not strictly medical but taking us along a bypath which is sometimes a pleasant change from the straight road of professional writing. Whether old age in itself should be regarded as a disease is a question about which there has been much debate. Its definition as "the period at which a man ceases to adjust himself to his environment" the author regards as true only of senility or morbid old age. Certainly a study of those who have reached a sunny old age to discover their method and philosophy of life is worth while, so that those who come after may profit thereby. What more delightful character is there than the genial old man who has seen many years but has not lost the savor of life? McC.

SURGICAL CLINICS OF NORTH AMERICA. St. Louis Number, Vol. II, No. 6. Pp. 289; 105 illustrations. Philadelphia: W. B. Saunders Company, 1922.

THIS, the St. Louis number, is presented to the readers as the work of twelve of the big men of that city. They have well maintained the high standard of the contributions for which the *Clinics* are famed. Each article adds something that is new, useful and instructive. The great feature in these *Clinics* is not the reported cases so much as it is the description of the way they are handled. Here, we readers can obtain the many little tricks in technic that can be obtained only by such articles so presented. E.

BLOOD TRANSFUSION. By GEOFFERY KEYNES, M.A., M.D. (CANTAB.), F.R.C.S. (ENG.), Second Assistant, Surgical Professorial Unit, St. Bartholomew's Hospital. Pp. 166; 13 illustrations. London: Henry Frowde, Hodder & Stoughton, 1922.

THE first chapter is devoted to a very complete and interesting review of the history of transfusion. The following chapters include the indications for transfusion, and the dangers incident to its employment are thoroughly discussed. The methods of direct and indirect transfusion are described, and the principles underlying the various technic are described in detail.

The volume is compact and gives all the information necessary to a complete understanding of the subject. A very complete bibliography is appended. S.

A TEXT-BOOK OF THE PRACTICE OF MEDICINE. By VARIOUS AUTHORS; edited by FREDERICK W. PRICE, M.D., F.R.S. (EDIN.), Senior Physician to the Royal Northern Hospital; Physician to the National Hospital for Diseases of the Heart, London; formerly Physician and Honorary Pathologist to the Mount Vernon Hospital for Consumption and Diseases of the Chest; Examiner in Medicine at the University of St. Andrews. Pp. 1753; 96 illustrations. London: Oxford Medical Publications, 1922.

THE editor of this volume states in his preface that, on account of the great advance in knowledge throughout the domain of medicine, it is impossible for any one authority to do full justice to the ever-widening field of medicine and that, therefore, a useful purpose might be served by the publication of a work of moderate compass and in one volume, compiled by specialists in the different branches of medicine. To the reviewer this seems eminently fit. It is certainly impossible for any one man to speak authoritatively on all the phases of internal medicine, and while such a man may be able to write on the various phases of medicine from his knowledge of the literature, he certainly cannot do it from first-hand practice in all the special branches of medicine. For this reason, it seems quite possible that the old style text-books of medicine may in time disappear, and be replaced by volumes such as the present one, which deal with the various diseases from the viewpoint of those who have made special study of this or that disease. This plan has been followed out in the large systems of medicine and the same scheme is followed in this one volume presentation of the subject of medicine. It is, in reality, a small system, although one hardly could call it small, as there are packed between the covers nearly two thousand pages of small print.

As with all systems, some of the sections are superior to others and some of the authors are better known than others but it does not follow that the best sections are always by the best known authors. In going over some of the diseases in most cases there seems to be a very complete exposition of the disorder. There is really a greater uniformity in the sections than one would think possible, when you consider that twenty-six different authors contributed to the volume. Taken as a whole the book can be recommended as an authoritative, complete and thorough handbook of medicine. M.

MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN (REPORT FOR THE YEAR 1921–1922). Edited by SIR WALTER M. FLETCHER, K.B.E., M.D., Sc.D., F.R.S., Secretary. London: H. M. Stationery Office, 1922.

THE great value of the research work fostered by the Medical Research Council has been more and more appreciated throughout the scientific world since its first publications in 1915. Not, however, until one carefully studies its latest annual report of 125 pages, does one realize the truly astounding amount of work that the Medical Research Committee (later Council) has been able to achieve or stimulate. From the first publication of their special report series in 1915 on "The Boot and Shoe Industry," this phase of their work alone has produced 72 careful studies, averaging from 30 to 300 pages in length, and scattered over such topics as tuberculosis, cerebrospinal fever, dysentery, alcohol, rickets, shock, venereal disease, industrial hygiene, pathological methods, biological standards, radium, etc., etc. In addition, they have aided many institutions and individual investigators with part-time grants, so that the present report alone names over 500 persons and 150 institutions with which they have had associations in the past year.

The National Research Institute, with which the Council is most directly concerned, received about one-quarter of the total budget for work in its six departments of Biochemistry and Pharmacology, Experimental Pathology, Bacteriology and Protistology, Applied Physiology, Applied Optics, Statistics and Library Publications, under the direction of eminent scientists, such as H. H. Dale, Capt. S. R. Douglas, Leondar Hill and J. E. Barnard.

The national collection of type cultures at the Lister Institute, the Standard Laboratory at Oxford, the Department of Clinical Research and the Cardiographic Department of the University College Hospital Medical School, the clinical research units at the London and St. Bartholomew's Hospitals, the work of Mellanby, Sir Almroth Wright, MacLean, Meakins, Starling, Laslett and Ivy Mackenzie are only a few of the important projects subsidized by the Medical Research Council.

Truly can one say that the annual grant of £130,000 has been wisely administered and that Parliament's Committee on National Expenditure showed wisdom in not cutting down their grant-in-aid even in these days of general retrenchment. K.

A Clinical Treatise on Diabetes Mellitus. By Marcel Labbé, M.D., Professor of General Pathology at the Faculty of Medicine of Paris and Physician to the Charité Hôpital: translated, revised and edited by Charles Greene Cumston, M.D., Lecturer at the Faculty of Medicine of the University of Geneva and Fellow of the Royal Society of Medicine of London. Pp. 382. New York: William Wood & Company, 1922.

It is like carrying coals to Newcastle to translate such a book as this from the original French into English at the present time. The rapid advance of our knowledge concerning many aspects of the diabetic problem results in a book becoming out-of-date very quickly. It is true that the author has had a very large experience with diabetes, and his observations on the symptomatology of diabetes are valuable. For example, the chapters on "Diabetes and Tuberculosis," on "Edemas in Diabetes" and on the "Painful Syndromes in Diabetes" are all interesting but there is little mention of many of the chemical methods which we have learned to depend upon in this country. The translator also has unfortunately used many unusual words and phrases, as for example, "Social midst," "acromegalia," "larvate," "undosable," "ammonuria," and "hyperglycistia." In fact, there is little to recommend in this book. P.

Maladies de la Plèvre et du Médiastin. By Marcel Labbé, M.D., Professor, Faculty of Medicine of Paris; P. Menetrier, Professor, Faculty of Medicine of Paris; L. Galliard, Honorary Physician to the Hospital of Paris; F. Balzer, Physician to the Hospital St. Louis; and E. Boinet, Professor of the School of Medicine of Marseilles. Pp. 596; 114 illustrations. Paris: J. B. Baillière, 1922.

This extensive study offers much that is of value from a clinical point of view, while at the same time suffering from a failure to include references to the recent literature. There are many references given, few of which are to other than French literature. Most of the references date back ten or twenty years and the only recent ones are from the French literature. French clinicians

have always been peculiarly interested in diseases of the pleura and this present work is essentially a review of their studies. The article on pulmonary syphilis is especially interesting, for the French place much more emphasis on this subject than do our own writers. Another interesting chapter concerns adenopathies of the mediastinum. On the whole, however, the work offers little which cannot be obtained equally well from any one of the recent systems published in the English language. P.

Rickets. By J. Lawson Dick, M.D. (Edin.), F.R.C.S. (Eng.), Deputy Commissioner of Medical Services, London Region, Ministry of Pensions. Pp. 488; 7 full-page illustrations and numerous figures in text. New York: E. B. Treat & Co., 1922.

In this book the author has endeavored to build a background for the present-day scientific understanding of rickets. He has collected a wealth of information, geographical, ethnological, sociological and economic, to show that rickets is a disease pursuant to modern industrialism. While the latest studies on the effects of light deprivation are not included in the book, the author is convinced that housing conditions, which compel deficient light and fresh air, constitute the important factor in the etiology of the disease. The history of rickets is well considered; it is especially interesting how the disease, at first most common among the cultivated classes, came to be a disease of the laboring man's child. The book is very readable, being free of tedious tables of experimental data. The author presents his work as evidence to justify the sweeping reforms necessary for the elimination of rickets, if this theory of its causation be proved correct. S.

Physical Exercises for Invalids and Convalescents. By Edward H. Ochsner, B.S., M.D., F.A.C.S., President, Illinois State Charities Commission; Attending Surgeon, Augustana Hospital, Chicago. Second edition. Pp. 56; 42 illustrations. St. Louis: C. V. Mosby Company, 1922.

There are described forty-two exercises especially designed for the use of convalescents and invalids and persons engaged in sedentary occupations. They are so arranged as to give well-balanced exercise to the whole body, and no apparatus is required. The descriptions are clear and the illustrations adequate. K.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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AND

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Phenoltetrachlorphthalein Liver Function Test.—ROSENTHAL (*Jour. Am. Med. Assn.*, 1922, **79**, 2151) has introduced an important modification of the technic of the use of phenoltetrachlorphthalein in the estimation of liver function, depending on the study of the rapidity of the removal of the dyes from the circulation. After detailing the technic of the phenoltetrachlorphthalein test, he gives the results in 37 instances, comprising cases of known degree of liver damage. Ten cases are used as controls which were normal from a point of view of liver function, but which comprised diseases of practically all the other organs of the body. Five cases of carcinoma of the liver were tested; 3 cases of cirrhosis of the liver; 2 cases of acute hepatitis; 1 case of cholangitis and 1 of chronic passive congestion. Several cases of toxemia of pregnancy and 1 of acquired hemolytic jaundice were also tested. Rosenthal makes the following comment: "The normal liver removes phenoltetrachlorphthalein from the blood stream with rapidity and uniformity. The damaged liver takes up the dye much more slowly; large amounts may remain for a prolonged period in the plasma, where the dye can be accurately and quantitatively estimated. Experiments have shown that practically none of the dye is taken up by the red cells. In this series of cases of liver disease the abnormal results have not paralleled the degree of jaundice or hepatic enlargement. The highest degrees of retention have been present in acute hepatitis, in a case of cirrhosis in which there was a small liver, and in advanced cases of hepatic carcinoma. A fixed dosage of tetrachlorphthalein according to the body weight is used, so that a unit of work is imposed on each unit, by weight, of liver tissue. The normal curves show the time required

for the entire liver to perform this task. For these reasons, borne out by clinical and experimental observation, it seems probable that the test gives an index of the total amount of functioning liver tissue." This communication would appear to be of real importance, describing apparently a method of study of hepatic function decidedly more satisfactory than any which has yet been devised.

Relapsing Pyrexia in Hodgkin's Disease.—HALL and DOUGLAS (*Quar. Jour. Med.*, October, 1922, p. 22) report a case of anatomically proved Hodgkin's disease which showed regularly recurring attacks of pyrexia. They have examined the temperature records of other cases extending over long periods of time. They show that the time from the middle of one period of fever to the middle of the next (the pyrexial span) was found to vary between fifteen and twenty-five days in 80 per cent of the cases. In individual cases, however, the periodicity did not vary by more than five days and in many cases was of remarkable regularity. The *form* of the pyrexial wave in each individual case was fairly constant. Very low temperatures were often recorded in the apyrexial periods, at which time there was often an apparently complete symptomatic recovery. The charts show a gradual stepping upward and downward of the pyrexial waves. The authors observed in these characters of periodicity gradual ascent of fever, and low temperatures with apparent complete recovery between pyrexial periods. The disease shows a similarity to certain recurring fevers such as malaria, relapsing fever, rat-bite fever and trench fever. It differs from these in greater length of span. The similarities suggest the possibility of an organismal infection as the cause of this type of relaxing pyrexia.

Family Association of Cardiac Disease.—ST. LAWRENCE (*Jour. Am. Med. Assn.*, 1922, **79**, 2051) studied 100 families, each of which contained at least 1 child enrolled in the cardiac clinic of St. Lukes Hospital. Exclusive of the 100 children who formed the basis of study, there were 480 persons known to have had close and long-lasting contact with patients suffering from rheumatic heart disease. Seventy-one (14.8 per cent) of these "exposed" persons had a definite infection of the rheumatic group. 38 (8 per cent) had definite cardiac disease. These figures are much greater than those given for the incidence in the general population. A similar study of 100 families, each of which had at least 1 member the subject of tuberculous infection, showed very similar figures. The results of the investigation suggest that the intimate association of family groups may have an important relation to the spread of rheumatic heart disease, and that the family offers a place for the application of the available preventive measures.

Psychologic Tests Applied to Diabetic Patients.—MILES and ROOT (*Arch. Int. Med.*, 1922, **30**, 767) report the results of psychologic tests made on 39 diabetic patients, and give the figures for a corresponding number of controls. Diabetic patients frequently complain of poorer memory and power of attention, but objective proof of this has been lacking up to the present time. By certain psychologic tests applied in such cases as well as to suitable controls it was found that diabetic patients with hyperglycemia and glycosuria at the beginning of treat-

ment show a decrement of about 15 per cent or more in memory and attention tests. The loss is in amount rather than in quality. With treatment the diabetic improves rapidly in his psychologic status, approaching, but not quite reaching normal. In accuracy and quickness of movement 5 treated diabetics, each case of long duration, were 20 per cent below normal.

Chronic Nephritis Anemia.—BROWN and ROTH (*Arch. Int. Med.*, 1922, **30**, 817) from their study of 187 cases diagnosed chronic glomerular nephritis at the Mayo Clinic, report their observations on 105 of these cases which showed anemia. They present evidence to show that the anemia of uncomplicated chronic nephritis develops in the absence of blood loss (microscopic blood in the urine having no relation to the degree of anemia) and this anemia is not due to excessive hemolysis. They point out that this type of anemia cannot be attributed to increased concentration in the blood of any known nitrogenous substance. They believe that the bone marrow suffers damage concomitantly with renal, retinal and cardiac tissues. In a group of cases studied during the development of renal insufficiency, anemia developed four to six weeks after the onset of the renal injury. The tardiness of the anemia is explained on the basis of decreased formation of erythrocytes. The injury to the bone marrow concerns only its erythrogenetic function. Leukocytogenesis is not involved. They believe that the unknown agent causing renal insufficiency is probably the etiological factor in the disturbance of hematopoiesis, in other words, a common cause is present. Twenty cases of chronic glomerular nephritis in whom the red blood cell count was found to be below 3,500,000 per cm. showed a remarkably high death rate, 18 of the 20 dying within ten months and many of them within one month. The authors point out that an anemia of this degree has a prognostic value similar to that of creatinin retention.

SURGERY

UNDER THE CHARGE OF

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A Case of Congenital Osteosclerosis.—GHORMLEY, (*Johns Hopkins Hosp. Bull.*, December 1922, p. 444) says that the patient limped and complained of pain in the left hip. Repeated roentgenographs of all the bones were then made and showed much the same condition throughout the skeleton. Besides the curious density of the flat bones and the rather hazy outline along all the bones, the vertebral bodies showed a marked density at either pole. Definite thickening of the cortex of

all the long bones was noted as more marked in the femora and humeri. The skull was thicker than normal. In the femoral necks and especially in the left, there seemed to be a breaking down of the bone just below the epiphysis, so that the epiphysis had slipped inward and downward. Roentgenographs of the mother and father were then made, which showed the mother's bones to be normal; but practically the same condition existed in the father.

Salivary Glands in Carcinoma.—DUDGEON and MITCHINER (*Lancet*, September 2, 1022, p. 558) say that in the vast majority of cases of carcinoma of tongue and floor of mouth these glands are not the seat of carcinoma. In nearly all cases, the changes present in these glands are of a chronic inflammatory nature somewhat analogous to the changes met with in the pancreas in chronic pancreatitis and are apparently due to infection from the mouth along the ducts. In other cases, no microscopical change can be seen. The lymph nodes in this area show malignant change in only 27.3 per cent of early and 50 per cent of late cases, though inflammation is always present. It would appear, therefore, in certain cases with early carcinoma of the tongue, to be justifiable to leave the submaxillary area untouched at operation, though clinical experience teaches that the risk of the subsequent appearances of metastases is very great.

The Healing of Gastric Ulcer.—STEWART (*Brit. Med. Jour.*, 1922, **2**, 1164) says that healing of gastric and duodenal ulcer is a common event. Statistics are given to show that in the postmortem room scarring is met with almost as frequently as ulceration, while duodenal scars occur with about one-half the frequency of duodenal ulcers. This difference may be partly accounted for by the greater liability of duodenal ulcers to perforate. Single and multiple gastric scars are met with in the ratio of 4 to 1, which is exactly the same as the ratio of chronic to acute ulcers. It is suggested from this, that acute and chronic ulcers have an equally good chance of healing. Hour-glass contraction of the stomach is met with in about 6.5 per cent of all cases of completely healed gastric ulcer. There is no evidence from present observations that carcinoma arises in connection with gastric scars, whereas in a series of 98 stomach specimens received for microscopical examinations, the incidence of carcinoma in cases of simple chronic ulcer was 11.5 per cent.

The Diagnosis and Treatment of Bone Lesions.—BLOODGOOD (*Am. Jour. Roentgenol.*, 1923, **10**, 42) says that roentgenograms immediately after trauma to bones and joints are highly essential for a record of comparison if the trauma excites some benign or malignant pathological process. Moreover, roentgen-ray examination of multiple bone lesions would aid in differential diagnosis. When the roentgen-ray show multiple distinctly central lesions, one can practically exclude primary sarcoma. When distinct periosteal multiple lesion is found, malignancy can be excluded. Roentgenograms of the chest should be made routinely, for the author can cite evident metastases to lungs within three months of first symptoms of sarcoma. Moreover, he has not found tuberculosis of the lung in cases of sarcoma of bones.

Renal Torsion.—Brasch (*Jour. Urolog.*, 1923, **9**, 12) says that incomplete congenital rotation and acquired torsion of the kidney, while of anatomical interest, are of no clinical importance *per se*. The anomalous position of the renal pelvis and its relation to the ureter may, in certain cases, permit urinary obstruction by some extrarenal factor. Traumatic hydronephrosis without direct injury to the kidney, may occur following a fall or blow which is accompanied by renal torsion and fixation of the upper ureter by adhesions. Renal torsions without evident ptosis or other known etiological factors, may occasionally occur with a moderate degree of hydronephrosis.

Surgery in Patients with Obstructive Jaundice.—Walters (*Am. Jour. Surg.*, 1923, **37**, 2) says that postoperative intra-abdominal hemorrhage is often the cause of death in patients with obstructive jaundice. Moreover, the coagulation time of the blood should be determined before operation and if the time is lengthened beyond six minutes, an attempt should be made to reduce it by intravenous injections of calcium chloride. Calcium chloride given intravenously, reduces the coagulation time of the blood and combines with the bile pigments circulating in the blood stream, rendering them less toxic. The diminution in the supply of glucose to the tissues in the body as a result of the toxemia of the liver cell, is overcome by supplying glucose directly to the tissues by means of proctoclysis and subcutaneous injection.

Diverticula of Bladder in Children.—Hyman (*Surg., Gyn. and Obst.*, 1923, **36**, 27) says that vesical diverticula are rare findings in childhood, not more than 30 being found in a review of over 600 cases. However, diagnosis of this condition in children should present no difficulties. Little value can be placed on history. Physical examination of the abdomen is important. A chronically distended bladder, especially asymmetrical in outline, should make one suspicious of a diverticulum. The cystoscope and cystogram are absolutely essential in making a correct diagnosis. In the 3 reported cases there were no evidences of obstruction, either vesical or urethral. All 3 diverticula were in immediate proximity to the ureter; in 1, the ureter opened into the sac and as a result, the ureters were compromised to such a degree, as to cause obliteration of the lumen with resultant dilatation. Division of ureter with reimplantation was performed in all 3 cases, with recovery of the patients. The author feels that there will be an increase in the number of cases reported, as soon as cystoscopy in children is done more routinely. He feels that the presence of diverticula in patients so young without evidences of any obstruction, leads one to conclude that they were congenital and that in all probability, many of the diverticula in adults have also a similar origin.

Cancer of the Pharynx.—Jackson (*Ann. Surg.*, 1922, **77**, 1) says that certain curable laryngeal conditions are in some cases the sequential predecessors of frequently incurable cancers. The author feels that it is justifiable to use the word precancerous for such conditions as continual laryngeal irritation from chronic laryngitis, keratosis, syphilis, pachydermia, so-called prolapse of the ventricle and benign growths (occurring in a person of cancerous age). All these should be

cured surgically or otherwise. It is no argument against this life-saving rule to contend that these conditions are too rarely predecessors of cancer to justify regarding them as etiological factors in cancer. There is no known agent causative of any disease that will always, in all individuals under average conditions of exposure, produce that disease. There will be few deaths from laryngeal cancer when every member of the medical profession fully realizes the frequently malign nature of chronic hoarseness.

Pyelonephritis.—STERLING (*Jour. Urolog.*, 1923, **9**, 29) says that a large number of so-called surgical kidneys can be saved an operation by drainage and lavage of the kidney pelvis. At least 50 per cent of the cases of pyelonephritis are being treated for other conditions such as appendicitis, cholecystitis, duodenal ulcers, without the formality of a urinalysis. Careful elimination of the foci as well as other accessory factors, will clear up the majority of the kidney infections. Repeated search should be made of the urine for pus, as one negative urinary examination does not always eliminate the urinary tract. The colon bacillus usually crowds the streptococcus out, which has been demonstrated culturally, making it difficult to demonstrate it in the urine in these infections.

The Relation of Calcified Abdominal Glands to Urinary Surgery.—WALKER (*Lancet*, 1922, **2**, 1213) says that operation in 11 of 42 cases of painful calcified abdominal glands, resulted in the disappearance of the pain whether it had the form of constant aching or recurrent attacks of colic. Moreover, all these cases have remained free from pain since operation. The author believes that there is no longer any danger of general dissemination of the tubercle bacillus which is usually responsible for the condition, or probability of infection in the urinary tract. Tuberculous peritonitis is not a concomitant or a sequel of this condition and adhesions which might interfere with the action of the bowel, or form obstructing bands, do not form. Against any general rule of operation of these cases in children, is, however, the knowledge that recovery without operation must take place in the great majority of these cases without further trouble. Therefore, operation is only justifiable in those cases in which symptoms are severe and are proved to be directly due to the calcified glands. These cases can be selected only after investigation by thoroughly modern methods of examination.

The Question of Recurrent Calculi.—BARNEY (*Surg., Gynec. and Obst.*, 1922, **35**, 743) says that there is an unfortunate paucity of investigation on the matter of recurrent or overlooked renal calculi and it would be desirable to have various observers in different clinics undertake such investigations. Roentgenographic examination during or shortly after convalescence, is essential for the accuracy of the results in such work. The data at hand show that stones are subsequently found in the kidney after operation in a surprising number of instances. It is however impossible to say which are "recurrences" and which are "left overs." Actual recurrence is unquestionably very frequent. The complex character of the interior of the kidney, hemorrhage from its mucosa and the comparative inaccessibility of this

organ in many cases, contribute to the difficulties in removing all stones. The fluoroscope offers the most promising prospects for success in this work. Moreover, preoperative study cannot be too painstaking, nor must the possibility of superimposed shadows of calculi be overlooked. A second operation for the removal of remaining stones is advisable in most cases and should be done soon after first operation. Pyelotomy is unquestionably the operation of choice and is often advantageously combined with partial nephrectomy.

THERAPEUTICS

UNDER THE CHARGE OF

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Balancing the Diabetic Diet.—STROUSE (*Jour. Am. Med. Assn.*, 1922, **79**, 1899) summarizes the recent metabolic work in diabetes and presents a simple procedure for applying these principles clinically. It is necessary that certain data be first obtained. The basal metabolism, the basal caloric requirement calculated therefrom, the daily urinary sugar and nitrogen and the glucose tolerance must be determined. The protein ratio is then 0.66 gm. per kilogram of body weight. Inasmuch as 56 per cent of the protein is burned as carbohydrate, the carbohydrate ratio may be calculated by subtracting from the glucose tolerance 58 per cent of the protein. The basal caloric requirement being known from the determination of the basal metabolism plus 20 per cent for the specific dynamic action of protein and the energy requirements for a bed existence, the calories supplied by the protein and carbohydrate to be fed are calculated by multiplying the total grams of these two substances by 4.1. The remaining calories must then be supplied in fat and the fat in grams is calculated by dividing the caloric requirement by 9. This ratio of fat is comparatively high in proportion to the amounts used by Allen. The danger of acidosis must be guarded against and this is accomplished by the antiketogenic substances resulting from the combustion of protein and especially carbohydrate. The acidosis producing substances are ketogenic and there exists a definite relationship between the ketogenic substances of fat metabolism and the antiketogenic substances of protein and carbohydrate metabolism. This ratio may roughly be approximated when the ratio of fat in grams is to the available carbohydrate in grams (equal to carbohydrate tolerance as calculated above) as 2.5 to 4 is to 1. A diet so calculated will provide a comparatively low protein and high fat allowance. The patients maintained on such a diet were without significant clinical acidosis.

Cardiac Functional Tests.—BRITTINGHAM and WHITE (*Jour. Am. Med. Assn.*, 1922, **79**, 1901) have eliminated as of small value all but two of the many cardiac functional tests. These two were submitted to further study. Vital capacity determinations were made on 144 patients, 48 of whom had some cardiac complication; 16, some pulmonary complication and 80 had neither cardiac nor pulmonary disease. Of the 80 with no intrathoracic disease, 50 per cent had vital capacities at least 20 per cent below the calculated normal; in the cardiac group "most of those who had no congestive heart failure had normal vital capacities" while every one of the patients with congestive failure had a low vital capacity. The conclusion is reached that vital capacity determinations furnish measures of dyspnea more definite than "marked," "slight," etc., but rarely aid in the management or "sizing up" of the patient. The exercise tolerance test consisted in swinging from floor to overhead, two 20-pound dumbbells, a given number of times (15 and 20) in a given number of seconds (40 and 50), and determining the effects on blood-pressure. The test proved of no value for diagnostic or prognostic purposes generally, so far as the heart is concerned and is useful only in following the progress of the individual case. The test is therefore unsatisfactory as a cardiac efficiency test. Vital capacity and exercise tolerance determinations were markedly at variance in 14 per cent of the cases in which both tests were performed. The final conclusion reached by the authors is that there is no satisfactory test of cardiac functional efficiency at the present time.

PEDIATRICS

UNDER THE CHARGE OF

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Intraperitoneal Transfusion with Citrated Blood. An Experimental Study.—SIPERSTEIN and SANSBY (*Am. Jour. Dis. Children*, 1923, **25**, 107) have shown that freshly citrated blood injected into the peritoneal cavity of rabbits is absorbed. Necropsies at various intervals following the operation reveal that the quantity present in the abdominal cavity rapidly decreases in amount and that absorption of comparatively large amounts of blood is completed in three or four hours. Estimation of blood values demonstrates definite increases from the time the blood is transfused until the animal is killed. They have shown that the erythrocytes enter the blood stream without undergoing any morphological changes. Smears of the fluid in the abdominal cavity taken at necropsy show no change in the size, shape, and structure of the corpuscles, and no evidence of hemolysis. A rise in hemoglobin and cellular elements was seen following transfusion in normal and anemic animals, which cannot be accounted for by a mere concentration of the blood. Nucleated red blood cells of pigeons when injected

intraperitoneally into rabbits can be recovered from the general circulation in fifteen minutes, and can persist for at least twenty-four hours. They found that the erythrocytes enter the blood stream very rapidly. The increase in the blood values of the animals persisted for days. After severe hemorrhage the animals improved after the transfusion. No hemoglobinuria could be demonstrated. Autotransfusion and retransfusion have been successfully used in man. Clinical experience with cases of internal hemorrhage as compared to external hemorrhage tends to show that the blood is absorbed in a functioning condition. The intraperitoneal transfusion of citrated blood in rabbits is a safe procedure, simple to apply and efficient. Absorption of the blood takes place very rapidly, and a rabbit can apparently absorb approximately one-fifth of its own blood value in four hours. The intraperitoneal transfusion of citrated blood acts as a true transfusion, and not as the absorption of nutrient material.

The Effect of Olive Oil on Gastric Function as Measured by Fractional Analysis.—LOCKWOOD and CHAMBERLIN (*Arch. Int. Med.*, 1923, **31**, 96) in their experiments demonstrated that olive oil given before meals, as is usually done clinically, reduces the average total acidity about 12 per cent, and lowers the high point of the curve about the same degree. It causes a marked delay of the test meal in the stomach, and the oil is the last portion of the meal to be evacuated. When oil is given regurgitation of bile is five times as frequent as without it. They feel that the oil coats the food and mucous membrane whereby the usual local reflex action of the food is lessened. The presence of bile in the stomach usually means reversed peristalsis. This alone might account for the delay in emptying time. Alkaline duodenal regurgitation might also lower the acidity to the extent found.

Intracutaneous Reaction in Pertussis.—REISENFELD (*Jour. Am. Med. Assn.*, 1923, **80**, 158) studied 400 children in a large institution over a period of four years through several epidemics of pertussis. He had the opportunity of observing the disease with special reference to natural immunity, acquired immunity, and the diagnosis of the disease in its earliest stages and before the development of the characteristic spasmodic cough, whoop and vomiting. Children exposed in previous epidemics and not acquiring the disease were considered as possessing a natural immunity. Those giving the history of having had the disease before admission, or having had an attack of pertussis while in the institution, were grouped as those possessing an acquired immunity. The value of a method whereby it would be possible to designate children who had natural or acquired immunity, and to be able to diagnose pertussis in its earliest stages, can be readily appreciated. This was the motive of the author's study. Various preparations of Bordet-Gengou bacillus were employed. The reactions occurring in the Schick test for diphtheria were the standard of comparison. He injected 2 minims intracutaneously into the upper part of the flexor surface of the forearm. Sixty cases tested with pertussis vaccine gave 53 positive and 7 negative reactions. Thirty-nine cases tested with staphylococcus vaccine gave 35 positive and 4 negative reactions. Of 26 cases of active pertussis tested with pertussis vaccine, 14 reacted

positively within three hours, 19 in twenty-four hours and 7 in forty-eight hours. Twenty-five cases of active pertussis tested with staphylococcus vaccine gave 13 positive reactions in three hours, 20 in twenty-four hours, and 15 in forty-eight hours. No reaction was considered positive unless at least 5 mm. in diameter. As a result of his observations Reisenfeld found that no specific reactions were obtained by the use of various preparations of Bordet-Gengou bacilli injected intracutaneously to prove presence of the disease, or of a natural or of an acquired immunity. Positive and negative results alike were obtained in children having the disease, in children with an immunity, and in children developing the disease after the injection.

Malignant Tumors of the Suprarenal Gland.—STEVENS (*Jour. Am. Med. Assn.*, 1923, **80**, 171) reports a case in which there seemed to have been a definite connection between the trauma and the development of the hypernephroma. An early diagnosis was rendered difficult by the appearance of symptoms so soon after the injury, by the bleeding and hematoma found at the first operation, and because of the negative findings in the second operation. The patient's later symptoms, pigmentation of the skin, tumor mass, weakness and gastro-intestinal symptoms were suggestive of a tumor of the suprarenal gland. An interesting feature of this case was the brownish discoloration of the skin although only one of the suprarenal glands was affected. Another unusual feature was the comparatively slow progress of the disease. The majority of adrenal tumors progress rapidly after the first symptoms appear. Adenocarcinoma is infrequent in a patient so young. Until comparatively recent times the majority of both cortical and medullary growths were classed as sarcoma or lymphosarcoma. The latter are now considered to be of neuroblastic origin, and are termed neuroblastoma or neurocytoma. They are derived from the medullary portion of the gland and are seen during infancy or early childhood. In a study of 74 cases in which this case is included the following facts were elicited: Of 70 cases in which sex was mentioned, 42 males and 28 females were affected. Thirty-four per cent occurred in infants or young children, 18 per cent between six and forty years, and 48 per cent after forty years. The right suprarenal was involved in 41 per cent of the cases, the left in 45 per cent and both in 14 per cent. Tumor mass was palpated in 38 per cent; pigmentation occurred in 20 per cent; loss of weight was noted in 12 per cent; hematuria was observed in 9.5 per cent; elevation of temperature was seen in only 8 per cent. Premature sex development, principally overgrowth of hair, occurred in 8 per cent. Pus, albumin or casts were found in 7 per cent. Cases of successful extirpation have been reported.

After-care of Infantile Paralysis Cases of the 1916 Epidemic in Brooklyn.—DUNHAM and RILEY (*Jour. Am. Med. Assn.*, 1923, **80**, 224) report the results of their work in 300 cases. These patients did not come under care from the acute onset. The care of these individuals began from one to two years after the initial period of their illness, and as a result there was a great variety of physical defect, depending on the severity of the attack, the type of early treatment and the manner in which the parents coöperated with the physician. In this

group only 14 families had more than 1 child ill with this disease at the same time, which would strongly suggest that its contagion is not transmitted by methods obtaining in the common infectious diseases, since the vast majority of all other cases were in families with 2 or more children in the same household. The experience of that large epidemic should have taught that during an epidemic of infantile paralysis of any size of children with obscure indispositions should be kept at rest in bed for days until the exact nature of the condition can be determined. When paralysis occurs it usually appears a short time after the initial upset, the average in this series being three days. Often the paralysis comes on in from twenty-four to forty-eight hours. Early neglected cases should never be ignored in treatment later regardless of the degree of involvement. This is essentially a disease of childhood and every acute illness warrants a reserved diagnosis of acute poliomyelitis until later developments overrule this. Sporadic cases occur every year. In this series the back and abdomen, with both lower extremities, was the combination of involvement most frequently found. In the lower extremities the tibialis anticus was most often affected, next in frequency being the muscles of the calf and the tibialis posticus. In the upper extremities the biceps and the triceps were involved most frequently. The more severely involved upper extremities did not respond to treatment as readily as the equally involved lower extremities. Those patients made the best recoveries in return of function who had the least interference during the initial stage of the disease, and when treatment in the subacute and chronic stages was intelligently advised and faithfully carried out.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Clinical Test of a New Mercurial.—An excellent example of clinical approach to the problem of the efficiency of an antisyphilitic medicament is afforded by the report of COLE, DRIVER and HUTTON (*Jour. Am. Med. Assn.*, 1922, **79**, 1821) on Mercurosal, a proprietary mercurial for intramuscular and intravenous use, recently advertised to the profession as possessing special efficiency. The drug was employed on 38 patients in general accordance with the manufacturers' recommendations, but it was found it could be given somewhat more frequently. It was found to cause pain on intramuscular injection, to have some sclerosing effect on the vein, no general ill effect on the patient, less effect on syphilitic lesions than other familiar mercurials such as the biniodide and inunctions, no marked spirillicidal powers, in contradiction of the claims of the manufacturers, and no striking effect on the Wassermann reaction. In certain cases it failed to

produce improvement and was then replaced by the more familiar medicaments with benefit. In general it was apparent that the drug had no superiority and was in fact in some respects inferior to familiar non-proprietary preparations.

The Mechanism of Mercurial Stomatitis.—Two recent communications recall the important contributions of ALMKVIST to mechanism and treatment of mercurial stomatitis. *Acta Dermato-venereologica*, 1923, **1**, 312, contains an exceptionally complete review by this author of recent knowledge including the author's contributions (*Dermat. Wchnsch.*, 1922, **7**, 152) and an extensive bibliography. In a recent reply to a misquotation by Schreus, the author points out that a mercurial stomatitis is not produced by the irritant action of mercury in the saliva, as is so often supposed, but that bacterial action on the mucous membrane with the production of erosions and pockets is essential. The proteolytic bacteria, acting on food remains and accumulations about these pockets produce hydrogen sulphide, which penetrates or is absorbed by the mucous membrane. It then acts upon mercury in the tissue lymph, resulting in accumulations of mercury sulphide in the tissues, with subsequent necrosis and heightening of the bacterial action upon the necrosed tissue. The mercury sulphide formed in the blood is carried to the kidneys and excreted. A vicious circle is developed, with ulceration and extension. The proper point at which to attack the process is not by way of the mercury, but by way of the bacterial infection, through the cleaning and disinfection of the gum pockets and other accessible foci of bacterial infection in the mouth cavity, including the tonsillar crypts. Schreus advocates for treatment the Pfannenstiel method of administering sodium iodide and liberating nascent iodine in contact with the affected tissues by the local use of hydrogen peroxide, but the author states that this method has had extensive trial without any demonstrated superiority over peroxide alone. In the same issue of the *Dermatologische Wochenschrift* appears a communication from HAMMER (p. 158), describing a technic of treating the pockets, and suggesting that inhalation of mercury vapor such as occurs in the use of inunctions probably explains a greater frequency of stomatitis in this mode of administration. He has seen a case in which a laboratory worker developed the clinical picture of mercurial stomatitis from the inhalation of hydrogen sulphide. He has noted variations in the virulence of the mouth flora which he believes explain the occasional epidemic character of mercurial stomatitis.

Syphilis in French Africa.—In an elaborate study of syphilis in a subtropical country (French Africa) LACAPERE, (*Ann. des malad., vener.*, 1922, **17**, 561), discusses the incidence of neurosyphilis among the Mohammedans of Morocco, as compared with the incidence of neurosyphilis in France. He confirms earlier observations on the comparative rarity of late neurosyphilis among the Arabs, giving the incidence as approximately 5 per cent as compared with 30 per cent

in Fournier's estimates for France. He points out that in early syphilis there is a much less striking difference in the incidence of involvement of the nervous system in the two races; but that in later years of the infection, the two types seem to diverge, syphilis of the bones and skin becoming more common among the Arabs and syphilis of the nervous system among the Europeans. Among the early clinical manifestations, meningeal and cerebral lesions are approximately as common as in Europe. Hemiplegias, ocular paralysis, lesions of the cranial nerves and spastic paraplegia are the common late forms of neurosyphilis. Tabes and paresis are rare among the rural Mohammedan population and confined almost entirely to the mixed types of the large cities along the coast. Among the possible causes for this rarity of late neurosyphilis among the Arabs, the author rates the extremely early age at which the infection occurs. He considers that the embryonic and inactive condition of the nervous system at this earlier age diminishes the tendency to involvement. He emphasizes moreover, the absolute serenity and calm of the Arab life. He feels that the complete absence of nervous strain is influential in protecting the nerve structures. The extreme rarity of chronic alcoholism among native Mohammedans is also credited with some influence in protecting them from neurosyphilis. While none of these theories appear quite convincing, the statistical difference between the two races is apparent enough to need explanation.

Occupational Dermatitis.—GARDINER (*Brit. Jour. Dermat. and Syph.*, 1923, **34**, 297) discusses at considerable length the characteristics of occupational dermatitis. Among the interesting individual cases is one in which a lupus erythematosus-like eruption developed in a T. N. T. worker. Housewives, general laborers, iron and steel workers and colliery workers were most numerous among his patients in the order named. 63.6 per cent were found to have had preceding eruptive conditions on the skin. Seborrhea was the most important (28 per cent), and hyperhidrosis next (27 per cent). 77.4 per cent of the patients were shown to have some predisposing background in previous cutaneous conditions or general ill health. Alterations in materials in use in a given occupation may cause the development of the dermatitis in the case of a worker employed for many years at the same occupation. An attack of dermatitis may render a worker susceptible to something which he could previously resist. Spreading of the dermatitis may be from the irritant itself, or secondary infection. While attacks may commence in youth, they are more common over forty. In the less pronounced irritants, the gradual onset of the dermatitis may occupy a period of years and is usually most delayed in those types associated with seborrhea. Local traumatism is an important factor, and illness, the climacteric and old age are influential causative influences.

OBSTETRICS

UNDER THE CHARGE OF

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Fetal Death Before, During and After Birth.—This subject was discussed in the section on Obstetrics and Gynecology of the British Medical Association at its last meeting (*Brit. Med. Jour.*, 1922, **2**, 583). Ballantyne considered the difference in the method of respiration in the child before and after birth to be so great as to influence very markedly its pathology. The same difference in varying degree may be found between the functions of nutrition before birth and those established after birth. There is a period while the child is passing from its connection with the mother to its life in the external world, which is neither typically intra-uterine nor postnatal life, and during this period conditions originating in the uterus may develop. Such would be an infection or a process of degeneration. A fetus may also be so constituted as to be able to live within the mother's uterus, but unable to establish an independent external life. Stillbirth is commonly defined as the death of the fetus when viable, and in these cases maceration is often present. The causes of death in the fetus are those affecting the mother and transmitted to the child, such as the acute infections; those conditions developing in the mother which affect her ability to nourish the child, such as maternal toxemia and active and external poisons, like lead and alcohol. One recognizes that conditions developing in the appendages of the child, for example, the placenta and membranes, may cause its death; so may malformation. With a healthy placenta the child in the uterus is much safer from disease than after birth. The most important cause of fetal death during labor is prolonged and early rupture of the membranes. This not only tends to death from mechanical causes, as hemorrhage following pressure, but is especially apt to be followed by infection. The so-called complications of labor, placenta previa, separation of the placenta, prolapsed cord, disproportion, and unusual presentations and mechanisms, naturally influence fetal mortality during labor to a very great extent. As modern obstetric surgery has developed, direct injury to the fetus through unskilful interference and improper operations has very much lessened. So the destructive operations upon the child have been greatly reduced in frequency by the perfection of Cæsarean section. From all causes, the actual mortality of the fetus during labor has grown less. Fetal death any time during the stage of transition from intra-uterine to extra-uterine life has a pathology at present but little understood. The intra-uterine death of the fetus seems to depend in a considerable degree upon the pathology of the placenta; in proportion as this is sound the fetus is secure within the womb. It is not yet explained why the dead and retained fetus does not undergo putrefaction, and one does not know how a child can apparently be on the verge of death after delivery, and yet, ultimately develop to adult life. If maceration

were understood, we should know much more about the pathology of fetal death. In preventing the loss of the fetus, unusual and diseased conditions in the mother must be studied, and so far as possible remedied during pregnancy. Whatever points to an unnatural development of mother or child, whether from mechanical or other causes, must be rectified if possible. Too little importance has been placed in the past on the value of fetal life and with advances in obstetric science, it should be possible to greatly lessen fetal mortality. Syphilis threatens the fetus by rendering its bloodvessels so fragile that pressure or traumatism during labor is quickly fatal. While treatment during pregnancy may benefit the mother, if the child is subjected to mechanical interference during labor, the result may be fatal. In caring for the newborn child, especial attention must be given to the circumstances and character of its birth. After difficult labor not only does the mother but also the child demand unusual attention. In the city of Edinburgh under Ballantyne's supervision 138 women having venereal diseases were treated during pregnancy, and these women gave birth to 7 stillborn children. In contrast to these is a group of 33 who had no treatment during pregnancy, and who gave birth to 20 stillborn children. The lowest mortality rate was in patients cared for at prenatal clinics, free from venereal disease and delivered by the staff of the hospital. Among these patients the rate of fetal death was 5.9 per 1000; including patients with venereal disease under treatment during pregnancy the rate of fetal loss was 13.5 per 1000. One can form some idea of the results of treatment, by contrasting those cases where the mother had venereal disease during pregnancy, without treatment, with a fetal stillbirth rate of 606 per 1000, compared with those women who had no venereal disease and who received proper attention before the birth of the child, 5.9 per 1000. The success of treatment addressed to syphilis complicating pregnancy may be inferred from the rate of stillbirth in the children of such patients, which was 50.7 per 1000. In comparison with these may be taken the average percentage of stillbirth for the entire city, which was 47.7 per 1000. Although it is very difficult to obtain accurate statistics from the average hospital record, it is evident from every source that venereal disease and especially syphilis greatly increases fetal death, and that this condition can be greatly improved by prenatal care and by treatment addressed directly to the venereal disease.

Fetal Deaths During Labor.—HOLLAND (*Brit. Med. Jour.*, 1922, **2**, 588) asserts that more children are lost from complications in labor than from disease in either mother or child. In these cases there is no inherent pathological condition in the fetus, so that they might live and develop, if they could be carried through the dangers of birth. If these cases were classified so that the cause of death was given as maternal, placental or fetal, it might be of service. More than half (51 per cent) of deaths of the fetus are caused by some abnormal condition in the delivery, and hemorrhage is the most frequent of these, whether cerebral or visceral. That portion of the brain most injured is the tentorium cerebelli, and pertains especially to labor in breech presentation where, although delivery may be spontaneous, the child dies during or soon after birth. So frequent is this that 88 per cent is

stated as not an undue calculation. This suggests that in the birth of the aftercoming head, abundant time should be taken to guard the interest of the child. At least ten minutes should be allotted to this portion of labor.

The Influence of Toxemia in Causing the Death of the Child.—McIlroy (*Brit. Med. Jour.*, September 30, 1922) in treating of toxemia as a cause of death of the child reverts to the modern explanation of the toxemia of pregnancy, as the absorption of trophoblastic elements into the mother's blood, producing toxins, whose effects are better known than their composition. It is a familiar observation that the process of toxemia in the mother is shared by the embryo and fetus. Where the child is macerated this condition applies properly to changes in the tissues of the fetus only, and to understand the process present in the mother and child the placenta and membranes must be examined, when evidences of processes of degeneration will be found. The writer joins in the previous writer's plea for greater importance upon the life of the fetus as compared with the life of the mother. Without in any way desiring to neglect the mother, the interest of the fetus should receive more consideration. Of all the abnormal states which predispose to maternal toxemia, the retention of waste material in the bowels is held to be the most important. The modern theory of foci of infection is acknowledged as important; and not only constipation but deficiency in the action of the kidneys is recognized as having a powerful effect in the production of toxemia. That the ductless glands are important in determining the metabolism of mother and child is a familiar observation. The writer in making diagnoses in these cases would have the usual analyses of the urine and the blood supplemented by examination of the feces to determine the presence or absence of bacteria. The examination of the urine by chemical methods is far less important and satisfactory than has been believed. In the present stage of our knowledge a large percentage of urea in the blood is an indication of danger.

Disturbances of Vision Complicating Eclampsia.—Hirsch (*Monatsschr. für Geburts. u. Gyn.*, 1922, **59**, 141) describes the case of a woman suffering from eclampsia who was suddenly taken with loss of vision. This was temporary, lasting during the shortest interval for one hour and at the longest time for three days. No cause except the eclampsia could be found for this condition, and the examination of the eyes was negative. The question arose as to whether intra-cerebral condition might be present. Of this there is no positive proof. Prognosis in these cases so far as the vision is concerned is excellent, as patients regain fully normal vision. In none of these cases has there been a permanent injury to the sight. In 28 of these patients, 2 died from the eclampsia, 1 with rupture of the uterus as a complication. The disturbance of vision varies in degree with the severity of the eclamptic process, and from this ocular complication no idea can be gained of the severity of the eclampsia. It may be mild or excessively severe.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Effect of Injection of Active Deposit of Radium Emanation on Rabbits, With Special References to the Leukocytes and Antibody Formation.—Following previous studies on the effects of benzene, roentgen ray and thorium X on antibody formation, HEKTOEN and CORPER (*Jour. Infect. Dis.*, 1922, **31**, 306) inoculated rabbits intravenously with various-sized doses of the "active deposit" of radium emanation as used by Bagg. Total and differential counts were made of leukocytes before and at regular intervals after injection of the active deposit and if the animal died the tissues were carefully studied. The effect of the radium on antibody formation was determined by injecting 30 rabbits, intravenously, with 1.5 and 10 mc. four days before, coincident with, or five days after the intraperitoneal injection of about 10 cc of citrated sheep blood per kilo of body weight, and ascertaining the specific precipitin and lysin for sheep blood at regular periods afterward. The active deposit of radium emanation, given into the vein in salt solution, was lethal to rabbits in about six days in quantities exceeding approximately 8 to 10 mc. per kilogram weight. In lethal doses, the active deposit produced an initial leukocytosis, (as high as 34,600) which was followed by a marked diminution in the circulating leukocytes especially of the polymorphonuclears. This was associated with congestion in the liver, lungs, lymph glands, spleen, suprarenals and kidneys, frequently accompanied by capillary hemorrhages. The cells of the spleen, lymph nodes and bone-marrow often were decreased in number. It was noted, also that "the active deposit in non-lethal amounts may have a depressing effect on the formation of lysin and to a less extent on precipitin for sheep blood."

Study of the Action of Four Aromatic Cinchona Derivatives on Pneumococcus. A Comparison with Optochin.—FELTON and DOUGHERTY (*Jour. Exp. Med.*, 1922, **35**, 761) report the results of *in vitro* and *in vivo* experiments to ascertain the bactericidal activity and organotropism of chloroacetylanilide, p-chloroacetylaminophenol, m-chloroacteylaminophenol, 4-chloroacetylaminopyrocatechal and optochin, when pneumococci, Type I (Neufeld) was employed. The experimental animals were young white mice and rabbits. To avoid repetition of the long names of the first four drugs, which represent a uniform series of hydroquinine derivatives, the laboratory numbers, C 29, C 36, C 40 and C 110, respectively, will be used to refer to them. After extensive observations and comprehensive protocols, the authors

conclude in part, that all four of the aromatic cinchona derivatives have a rapid pneumococcidal activity both *in vitro* and in the peritoneal cavity of mice, and to a lesser degree in rabbits. In comparison, optochin (ethylhydrocuprein) is slower in action but its power is not so easily destroyed either *in vitro* or *in vivo*. In comparing the rapidity of *in vitro* bactericidal action and the intraperitoneal toxicity, C 29 exhibited the most rapid pneumococcidal action and was the most toxic for mice. C 36 was one-fifth as toxic as C 29 and only one-tenth less active bactericidally. C 40 was one-half as toxic and had about the same bactericidal power, while C 110 was one-eighth as toxic and one-fifth as pneumococcidal. Optochin was one-sixth as toxic and had one-fifth the bactericidal action. Arranged in the order of their ability to kill pneumococci when injected simultaneously with them into the peritoneal cavity, the drugs were C 40, C 110, C 36, optochin and C 29. While the chemotherapeutic action of the aromatic compounds was essentially local in character, a certain degree of diffusion was shown by administration per os, C 40 and C 110 having approximately the same value as optochin. When injected intravenously in small doses the drugs destroyed to a greater or less extent the natural defenses of the animal, optochin being perhaps less injurious than the others. The maximum tolerant dose, given intraperitoneally in a single dose, was not so efficacious as the same dose divided in fifths and inoculated at hour intervals. Under these conditions, optochin was not so active as the aromatic compounds. There was found to be a zone between the therapeutic and toxic doses, both single and repeated, for all the chemicals alike, where the natural resistance of the animal to an infection was reduced. This effect was noted particularly with C 29, C 36 and C 40. With optochin, the therapeutic dose was nearer the toxic than with C 110, C 36 and C 40.

Distribution of Potassium in Normal and Pathological Kidney.—By means of the Macallum potassium reagent, MENTEN (*Jour. Med. Res.*, 1922, **43**, 323) compared the microchemical distribution of potassium in kidneys from normal rabbits with those from animals receiving mercuric chloride. In the former a preponderance of potassium was observed in the convoluted tubules and ascending limb of the loop of Henle, while a relatively small amount was noted in the glomeruli and collecting tubules. The rods of Heidenhain were enveloped in a thin film of potassium. The normal nuclei were invariably free from any trace of this element. Furthermore, the minimum reaction occurred in the resting condition of the cell. After degenerative changes had been produced in the kidney by intravenous injections of mercuric chloride (and many other heavy metals), the amount of potassium was much augmented and the increment of increase was found always to be greatest in the convoluted tubules. No appreciable increase was noted in the glomeruli, which fact would seem to favor the theory of secretion of the urinary potassium salts by the tubules rather than of their filtration in dilute aqueous solution through the glomerulus with subsequent reabsorption of the excess water by the tubules. The cytoplasm of the necrobiotic cell contained a maximum amount of potassium, which substance could also be demonstrated in variable amounts in the nuclei of such cells. Experiments showed that the

increased amount of demonstrable potassium salts found in the injured cells was due to a liberation of the so-called "masked" salts, that is, those absorbed in the normal state, and that the transformation of these absorbed inorganic salts from the un-ionized to the ionized condition was intimately related to changes in surface tension of certain structural elements within the cells.

Device for Tubing Cooked Meat Medium.—To introduce meat medium into test tubes in a clean and rapid manner, HOLMAN (*Jour. Bacteriol.*, 1923, **8**, 47) uses the ordinary automobile grease gun. The front cap and nozzle are unscrewed and the barrel filled with the meat. The nozzle must not have too small a diameter, and must reach past the middle of the tube. The fluid portion is added to the meat particles through the ordinary tubing funnel. The medium is made from ground meat, preferably skeletal muscle, to which is added an equal quantity of water. This is mixed, sterilized, neutralized, and allowed to stand over night. The fat is then skimmed off, the medium tubed as described above, the fluid being added last, and it is then autoclaved at 120° C. for thirty minutes. The author points out that this medium keeps sterile for days, and that it is not necessary to boil and cool immediately before use as was formerly believed. "(Unless for very special purposes) Nor need the surface be covered with oil or paraffin. Complete mixing of the seeded material with the meat particles is the most important point." The author believes that "the simplicity of preparation, tubing and sterilizing, its wide range of use in the growth of bacteria, and its keeping qualities should make cooked meat the medium of choice for routine bacteriological studies."

The Use of Phenol-red and Brom-cresol-blue as Indicators in the Bacteriological Examinations of Stools.—After a series of investigations to determine the efficacy of phenol-red and brom-cresol-purple as indicators in differentiating between B. coli and members of the typhoid-dysentery group, CHESNEY (*Jour. Exper. Med.*, 1922, **35**, 181) found that a 3 per cent beef-extract agar cleared with egg to which 1 per cent lactose had been added from sterile 20 per cent solution, gave the best results. In the instance of phenol-red, the optimum reaction was a hydrogen-ion concentration of pH 7.6 to 7.8 and the optimum amount was 10 cc of a 0.04 per cent aqueous solution for every 100 cc of agar. With this indicator, the typhoid, paratyphoid and dysentery (Shiga, Flexner and His-Y) bacilli produce pink colonies, while the colon bacilli assume a bright green or yellow-green colonies, and the colonies are more opaque. The optimum reaction for brom-cresol-purple was pH 7.2 to 7.4, and the optimum amount was 5 to 8 cc of a 0.04 per cent aqueous solution for every 100 cc of agar, the colon bacilli producing greenish-yellow colonies, with a yellow zone, while the typhoid-dysentery group produced bluish colonies. It was found that either indicator could be used in conjunction with brilliant green in the amounts advocated by Krumwiede, without exercising any inhibitory effect upon the restraining powers of the brilliant green. Of the two indicators, brom-cresol-purple gave the sharper differentiation, and, the author states, is to be preferred.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF
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The Effect of Gasoline Fumes on Dispensary Attendance and Output in a Group of Workers—SPENCER (*Public Health Reports*, 1922, **39**, 2291) states that the gasoline fumes liberated in the workroom studied had produced cases of mild chronic gasoline poisoning. In workrooms where the ventilation is not adequate the liberation of gasoline fumes from open containers or from processes will, sooner or later, depending upon the amount and the concentration of the fumes, produce cases of acute, mild chronic or chronic gasoline poisoning. The liberation of gasoline fumes above an undetermined concentration, in an improperly ventilated workroom, will result in increased dispensary attendance and absenteeism among the workers exposed. Increased production and a lower rate of dispensary attendance were obtained by the removal of the gasoline fumes.

Malaria Control Operations in Relation to the Ultimate Suppression of the Disease.—BASS (*Jour. Am. Med. Assn.*, 1922, **79**, 277) states that malaria has disappeared from large areas in this country and in other parts of the world, chiefly as a result of development of the country, including drainage and clearing of the forest, incidental to agricultural and other industrial pursuits. Malaria prevalence is slowly but surely decreasing over practically all of this country, as a result of the steady march of civilization and settlement of the country. This process may be aided and hastened by anti-mosquito measures or the proper use of quinine. Health agencies are interested in encouraging these measures. The only part of the present malaria control activities that actually lead to ultimate suppression of the disease is permanent drainage and filling operations. All others are temporary and must be continued indefinitely, or the tendency will be toward a return to former conditions. The cost of intensive anti-mosquito operations for malaria control is so great that they have not been applied to a sufficiently large part of the total malarious area of the country to affect seriously the total prevalence of the disease. The cost of such malaria control as results from infected persons taking proper quinine treatment does not involve any cost over the amount that would be spent for other remedies. Therefore, it is applicable to the malaria problem of the country as a whole, and should be emphasized and encouraged by health agencies interested in malaria control.

The Scope of the Problem of Industrial Hygiene.—HAMILTON (*Pub. Health Rep.*, 1922, **37**, 2604) dwells on the extent and complexity of the problem. In discussing dust in relation to mortality and morbidity, it is emphasized that the quality of the dust is largely the determining factor in the hazard. Granite and flint dusts are very dangerous, while marble, sandstone and Portland cement are relatively harmless. Of organic dusts but little is known. Of poisons, benzol causes both acute and chronic poisonings. Specific fields in which our knowledge is very limited are mentioned.

The Responsibility of the Employer for the Health of the Worker.—JACKSON (*Pub. Health Rep.*, 1922, **37**, 2613) considers that the employer should provide: (1) Suitable, safe and healthful working places; (2) well-guarded machinery, tools and processes; (3) suitable foremen and supervisors; (4) suitable placing of each employee to best utilize his or her abilities; (5) protection from communicable diseases; (6) prevention and treatment of injuries; (7) time for rest and recuperation.

The Incubation Period of Typhoid Fever.—MINER (*Jour. Infect. Dis.* **31**, 3, 296) states that the incubation period of typhoid fever is highly variable, ranging in cases studied from three to thirty-eight or forty days. The mean incubation period in different epidemics ranges from 7 plus or minus 0.26 to 19.50 plus or minus 0.31 days, differing significantly from one epidemic to another. The standard deviations range from 1.84 plus or minus 0.18 to 8.85 plus or minus 1.17. The distributions are positively askew. The results obtained are consonant with the belief that the length of the incubation period depends in part on the virulence of the infection. The means of the epidemics due to infected water are 13.81 plus or minus 0.83, 19.38 plus or minus 1.66, and 19.50 plus or minus 0.31, whereas the means for those due to infected food, in which the dose was probably more massive are 7 plus or minus 0.26 and 9.54 plus or minus 0.39.

Detection of Typhoid Carriers.—GEHLEN (*Jour. Am. Med. Assn.*, 1922, **79**, 516) states that the State Board of Health of Minnesota, directly through its own representatives or through the local health officer, gives such instructions to be followed by the carrier and members of his family as are necessary for their protection and that of other associates, and explains the State law, which forbids a carrier to engage in the handling of any part of the public's food supply which may be consumed without being cooked after handling. The local health officer is charged to keep the State Board of Health informed as to any change in the carrier's residence or occupation, and, as long as the carrier obeys directions, all publicity is avoided. In 1 instance only has it been necessary to prosecute a carrier for illegally returning to a forbidden occupation. Three carriers, 1 a dairy woman, another a restaurant keeper, and the third a practical nurse and housekeeper, were forced to abandon their chosen occupations, the nurse-housekeeper having no income aside from her earnings for the support of herself an one dependent. Such restrictions of individual rights and liberty are

necessary to protect the public against these innocent distributors of disease and death. Since 1915, the Minnesota State Board of Health has been entrusted by the legislature with the disbursement of a special fund for the support of a typhoid carrier who, after unauthorized newspaper publicity, was unable to obtain work. Should not the State offer compensation to carriers who must give up their chosen occupation in order to protect its citizens?

The Place of Venereal-disease Control in Industry.—The loss of time and efficiency due to venereal diseases is considered by LAWRENCE (*Pub. Health Rep.*, 1922, **37**, 2609), and examples given in which syphilis of employees led to a serious risk to life and property.

Vaccination of Monkeys against Pneumococcus Type I Pneumonia by Means of Intratracheal Injection of Pneumococcus Type I Vaccine.—CECIL and STEFFEN (*Pub. Health Rep.*, 1922, **37**, 2735) show that experimentally in monkeys it is possible to induce immunity against Type I pneumonia by means of intratracheal injections of vaccine. They believe that the immunity is in great part cellular, as the serums of protected animals had almost no demonstrable protective bodies. Spraying with the vaccine was not effective in inducing immunity.

Tuberculosis Among the Ex-service Men.—CUMMING (*Pub. Health Rep.*, 1922, **37**, 2241) discusses the problem of cure for the tuberculous former service men which was presented after the Great War. Approximately the same incidence occurred as was to be expected in the same age group of males of the general population. A surprisingly high incidence of non-pulmonary tuberculosis was noted, chiefly involvement of the bones and joints. The administrative features of the problem are described.

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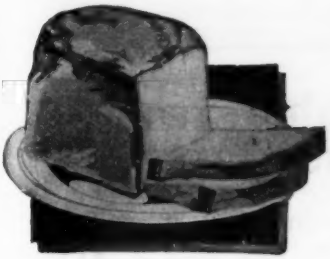

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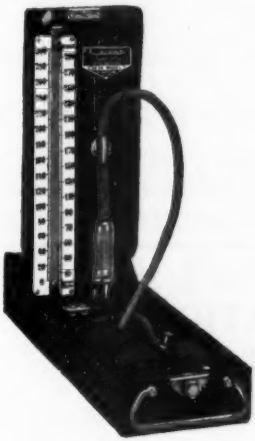

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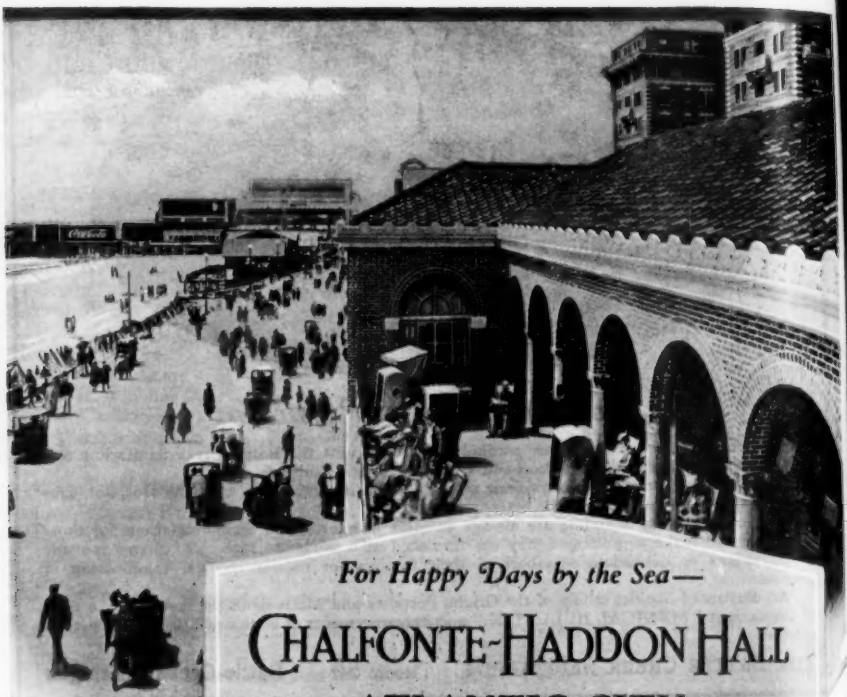

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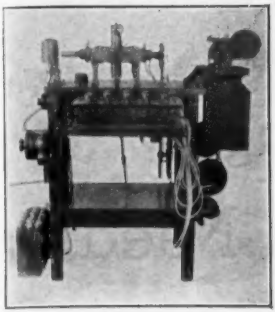

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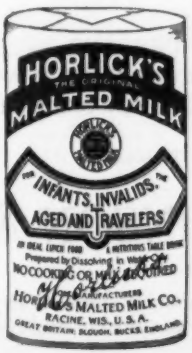

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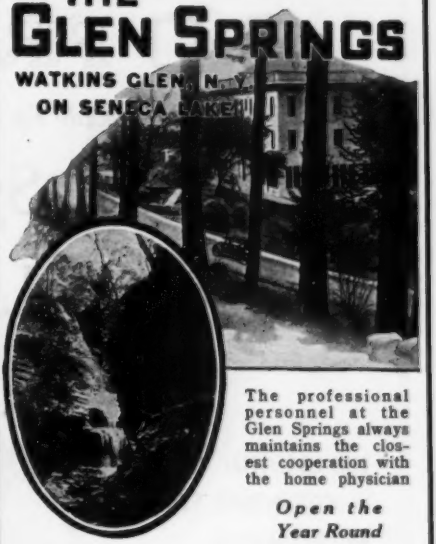

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